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(54) Title: THERAPEUTIC USES OF PPAR MEDIATORS

(57) Abstract: Use of PPAR mediators, and their pharmaceutical compositions, as ATP binding cassette transporter 1 (ABC-1) expression modulators, wherein the PPAR ligand receptor agonists of this invention are useful as inducers of ABC-1 expression.

Peroxisome proliferators activate PPAR , which acts as a transcription factor, and causes differentiation, cell growth and proliferation of peroxisomes. PPAR activators are also thought to play a role in hyperplasia and carcinogenesis as well as altering the enzymatic capability of animal cells, such as rodent cells, but these PPAR activators appear to have minimal negative effects in human cells (Green, Biochem. Pharm. 43(3):393, 1992). Activation of PPAR results in the rapid increase of gamma glutamyl transpeptidase and catalase.

It is also known that PPAR agonists inhibit the inducible nitric oxide synthase (NOS) enzyme pathway and thus can be used in the therapeutic intervention of a wide variety of inflammatory diseases and other pathologies (Colville-Nash, et al., Journal of Immunology, 161, 978-84, 1998; Staels et al, Nature, 393, 790-3, 1998).

PPARα is activated by a number of medium and long-chain fatty acids and is involved in stimulating β-oxidation of fatty acids in tissues such as liver, heart, and brown adipose tissue (Isseman and Green, supra; Beck et al., Proc. R. Soc. Lond. 247:83-87, 1992; Gottlicher et al., Proc. Natl. Acad. Sci. USA 89:4653-4657, 1992). PPARα activators are also involved in substantial reduction in plasma triglycerides along with moderate reduction in LDL cholesterol, and they are used particularly for the treatment of hypertriglyceridemia, hyperlipidemia and obesity. PPARα is also known to be involved in inflammatory disorders. (Schoonjans, K., Current Opionion in Lipidology, 8, 159-66, 1997).

The human nuclear receptor PPARδ has been cloned from a human osteosarcoma cell cDNA library and is fully described in A. Schmidt et al., Molecular Endocrinology, 6:1634-1641 (1992), the contents of which are hereby incorporated herein by reference. It should be noted that PPARδ is also referred to in the literature as PPARβ and as NUC1, and each of these names refers to the same receptor. For example, in A. Schmidt et al., Molecular Endocrinology, 6: pp. 1634-1641, 1992, the receptor is referred to as NUC1. PPARδ is observed in both embryo and adult tissues. This receptor has been reported to be involved in regulating the expression of some fat-specific genes, and plays a role in the adipogenic process (Amri, E. et al., J. Biol. Chem. 270, 2367-71, 1995).

Atherosclerotic disease is known to be caused by a number of factors, for example, hypertension, diabetes, low levels of high density lipoprotein (HDL), and high levels of low density lipoprotein (LDL). It has recently been discovered that PPARδ agonists are useful in raising HDL levels and therefore useful in treating atherosclerotic diseases (Leibowitz et al.;

Hyperinsulinemia is also linked to insulin resistance, hypertriglyceridaemia and increased plasma concentration of low density lipoproteins. The association of insulin resistance and hyperinsulinemia with these metabolic disorders has been termed "Syndrome X" and has been strongly linked to an increased risk of hypertension and coronary artery disease.

Metformin is known in the art to be used in the treatment of diabetes in humans (US Patent No. 3,174,901). Metformin acts primarily to decrease liver glucose production. Troglitazone® is known to work primarily on enhancing the ability of skeletal muscle to respond to insulin and take up glucose. It is known that combination therapy comprising metformin and troglitazone can be used in the treatment of abnormalities associated with diabetes (DDT 3:79-88, 1998).

PPAR γ activators, in particular Troglitazone®, have been found to convert cancerous tissue to normal cells in liposarcoma, a tumor of fat (PNAS 96:3951-3956, 1999). Furthermore, it has been suggested that PPAR γ activators may be useful in the treatment of breast and colon cancer (PNAS 95:8806-8811, 1998, Nature Medicine 4:1046-1052, 1998).

Moreover, PPARγ activators, for example Troglitazone®, have been implicated in the treatment of polycystic ovary syndrome (PCO). This is a syndrome in women that is characterized by chronic anovulation and hyperandrogenism. Women with this syndrome often have insulin resistance and an increased risk for the development of noninsulin-dependent diabetes mellitus. (Dunaif, Scott, Finegood, Quintana, Whitcomb, J. Clin. Endocrinol. Metab., 81:3299, 1996.

Furthermore, PPARγ activators have recently been discovered to increase the production of progesterone and inhibit steroidogenesis in granulosa cell cultures and therefore may be useful in the treatment of climacteric. (United States Patent 5,814,647 Urban et al. September 29, 1998; B. Lohrke et al. Journal of Edocrinology, 159, 429-39, 1998). Climacteric is defined as the syndrome of endocrine, somatic and psychological changes occurring at the termination of the reproductive period in the female. The menstrual irregularities are episodes of prolonged menstrual bleeding caused by a loss of ovulation. The loss of ovulation is caused by a failure of development of ovarian follicles.

Although peroxisome proliferators, including fibrates and fatty acids, activate the transcriptional activity of PPAR's, only prostaglandin J_2 derivatives such as the arachidonic acid metabolite 15-deoxy-delta^{12},14 -prostaglandin J_2 (15d-PGJ_2) have been identified as natural

been described in European patent application EP 99.402 668.0., filed on October 26, 1999, the contents of which are hereby incorporated herein by reference.

PPARα and PPARγ are transcription factors expressed in human macrophages (Chinetti, G. et al., J. Biol. Chem. **273**, 25573-25580 (1998)) and are known to modulate lipoprotein metabolism. For example, activation of the PPAR pathway increases the level of HDL-cholesterol (Pineda Torra, I., Gervois, P. & Staels, B., Curr. Opin. Lipidol. **10**, 151-159 (1999)). Patients who have Tangiers disease lack the functional ABC-1 and are defective in cholesterol efflux (Remaley, A.T. et al., Proc. Natl. Acad. Sci. USA **96**, 12685-12690 (1999)).

Cholesterol is the metabolic precursor of steroid hormones and bile acids as well as an essential constituent of cell membranes. In humans and other animals, cholesterol is ingested in the diet and also synthesized by the liver and other tissues. Cholesterol is transported between tissues in the form of cholesteryl esters in LDLs and other lipoproteins.

High-density lipoproteins (HDL) are one of the four major classes of lipoproteins circulating in blood plasma. These lipoproteins are involved in various metabolic pathways such as lipid transport, the formation of bile acids, steroidogenesis, cell proliferation and, in addition, interfere with the plasma proteinase systems.

HDLs are perfect free cholesterol acceptors and, in combination with the cholesterol ester transfer proteins (CETP), lipoprotein lipase (LPL), hepatic lipase (HL) and lecithin:cholesterol acyltransferase (LCAT), play a major role in the reverse transport of cholesterol, that is to say the transport of excess cholesterol in the peripheral cells to the liver for its elimination from the body in the form of bile acid. It has been demonstrated that the HDLs play a central role in the transport of cholesterol from the peripheral tissues to the liver.

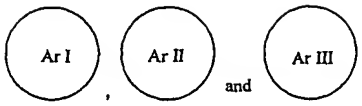
Various diseases linked to an HDL deficiency have been described, including Tangier and/or FHD disease, HDL deficiency, LCAT deficiency, and Fish-Eye Disease (FED). In addition, HDL-cholesterol deficiencies have been observed in patients suffering from malaria and diabetes (Kittl et al., 1992; Nilsson et al., 1990; Djoumessi, 1989; Mohanty et al., 1992; Maurois et al., 1985; Grellier et al., 1997; Agbedana et al., 1990; Erel et al., 1998; Cuisinier et al., 1990; Chander et al., 1998; Efthimiou et al., 1992; Baptista et al., 1996; Davis et al., 1993; Davis et al., 1995; Pirich et al., 1993; Tomlinson and Raper, 1996; Hager and Hajduk, 1997, Kwiterovich, 1995, Syvanne et al., 1995a, Syvanne et al., 1995b, and French et al., 1993). The deficiency involved in Tangier and/or FHD disease is linked to a cellular defect in the

uncontrolled uptake of cholesterol by recruited macrophages) and accumulation of fibrous tissue. The atheromatous plaque protrudes markedly from the wall, endowing it with a stenosing character responsible for vascular occlusions by atheroma, thrombosis or embolism, which occur in those patients who are most affected. These lesions can lead to serious cardiovascular pathologies such as infarction, sudden death, cardiac insufficiency, and stroke.

Applicants have discovered that PPAR activators induce ABC-1 expression in humans cells. In addition, Applicants have discovered that PPAR activators decrease lipid accumulation, by increasing apoAI-induced cholesterol efflux from normal macrophages. . This discovery identifies a central role for PPARs in the control of the reverse cholesterol transport pathway by inducing ABC-1 mediated cholesterol removal from human macrophages.

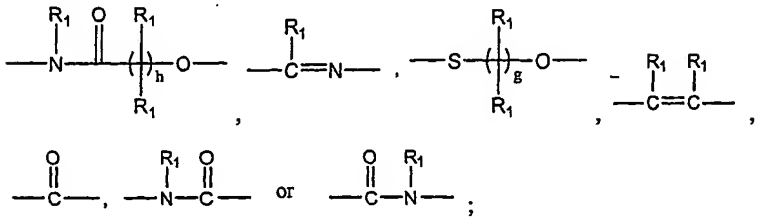
Therefore, the present invention discloses the use of PPAR mediators, and their pharmaceutical compositions, in regulating ATP binding cassette transporter 1 (ABC-1) expression, as well as a number of therapeutic uses associated with it.

PPAR mediators useful for practicing the present invention, and the methods of making these compounds are described herein or are disclosed in the literature, for example Nafenopin (US Pat. No. 5,726,041), UF-5 (WO 97/36579), ETYA: 5,8,11,14-eicosatetraynoic acid (Tontonez et al., Cell 79:1147-1156 (1994), it also purchasable from Sigma), GW2331: 2-(4-[2-(3-[2,4-difluorophenyl]1-1heptylureidoethyl]phenoxy)-2-methylbutyric acid (Sundseth et al., Proc. Natl. Acad. Sci. USA, 94, 4318, 1997), 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (Lohrke et al., Journal of Endocrinology 159, 429, 1998) AD 5075, clofibric, linoleic acid (Tontonoz et al. Cell, 79, 1147, 1994), BRL-49653: 5-[4-{2-[N-Methyl-N-(pyridin-2-yl)amino]ethoxy}benzyl]-thiazolidine-2,4-di one, (Japanese Patent Kokai Application No. Hei 1-131169 and in U.S. Pat. Nos. 5,002,953, 5,194,443, 5,232,925 and 5,260,445), fenofibrate, WR-1339: Tyloxapol®, (Lefebvre et al. Arteriosclerosis, Thrombosis, and Vasclular Biology, 17, 9, 1977), Pioglitazone: 5-{4-[2-(5-Ethylpyridin-2-yl)ethoxy]benzyl }thiazolidine-2,4-dione, (Japanese Patent Publication No. Sho 62-42903 and No. Hei 5-66956, U.S. Pat. Nos. 4,287,200, 4,340,605, 4,438,141, 4,444,779 and 4,725,610), Ciglitazone, (Lehmann et al. The Journal of Biological Chemistry, 270, 22, 12953, 1995), Englitazone: 5-(2-Benzyl-3,4-dihydro-2H-benzopyran-6-ylmethyl)-thiazolidine-2,4-dione (Japanese Patent Publication No. Hei 5-86953 and U.S. Pat. No. 4,703,052); Troglitazone: 5-[[4-[3,4-dihydro-6-hydro-6-hydroxy-2,5,-7,8-tetramethyl-2H-1-bnzopyran-2-yl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione (U.S. Patent No. 4,572,912),

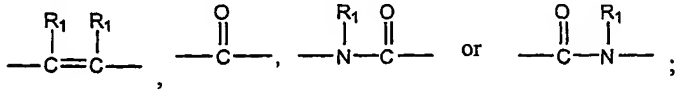


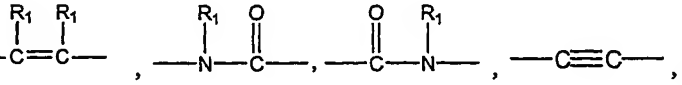
are independently aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, heteroaryl, fused heteroarylcycloalkenyl, fused heteroarylcycloalkyl, fused heteroarylheterocyclenyl, or fused heteroarylheterocyclyl;

A is O, S, SO, SO_2, NR_5, a chemical bond,

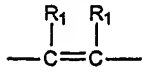


B is O, S, SO, SO_2, NR_4, a chemical bond,



D is O, S, NR_4,  or a chemical bond;

E is a chemical bond or



a is 0-4;

b is 0-4;

c is 0-4;

d is 0-5;

e is 0-4;

f is 0-6;

g is 2-4;

h is 0-4;

Brief Description of the Figures:

Figure 1 represents a Northern blotting analysis of up-regulation of ABC1 expression of THP-1 cells using RPR64 and RPR52 at different concentrations.

Figure 2 represents the corresponding bar graph of Figure 1 of up-regulation of ABC1 expression of THP-1 cells with RPR64 and RPR52 at different concentrations.

Figure 3 represents a standard curve ABC1 standard curve with TaqMan 5P primer/probe set.

Figure 4 represents a Northern blotting analysis of up-regulation of ABC1 in primary hepatocytes using Fenofibric acid and Wy 14,643.

Figure 5 represents a Northern blotting analysis of up-regulation of ABC1 in human monocytes derived macrophages using Fenofibric acid, PG-J2 and Wy 14,643.

Figure 6 represents a bar graph of apolipoprotein A-I-mediated cholesterol efflux in human macrophages using AcLDL, Wy 14,643 and AcLDL + Wy 14,643.

As employed above and throughout the disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

Definitions

In the present specification, the term "compounds for use according to the invention", and equivalent expressions, are meant to embrace compounds of general Formula (I) as hereinbefore described, which expression includes the prodrugs, the pharmaceutically acceptable salts, and the solvates, e.g. hydrates, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits. For the sake of clarity, particular instances when the context so permits are sometimes indicated in the text, but these instances are purely illustrative and it is not intended to exclude other instances when the context so permits.

"Prodrug" means a compound which is convertible in vivo by metabolic means (e.g. by hydrolysis) to a compound of Formula (I), including N-oxides thereof. For example an ester of a compound of Formula (I) containing a hydroxy group may be convertible by hydrolysis in

different, and include halo, carboxy, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, aryl, alkoxy, alkoxycarbonyl, aralkoxycarbonyl, heteroaralkoxycarbonyl, Y^1Y^2NCO-, wherein Y^1 and Y^2 are independently hydrogen, alkyl, aryl, aralkyl or heteroaralkyl, or Y^1 and Y^2 taken together with the nitrogen atom to which Y^1 and Y^2 are attached form heterocyclyl. Exemplary alkyl groups include methyl, trifluoromethyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, n-pentyl, and 3-pentyl. Preferably, the alkyl group substituent is selected from acyl, carboxy, carboxymethyl, methoxycarbonylethyl, benzyloxycarbonylmethyl, and pyridylmethyloxycarbonylmethyl and alkoxycarbonyl.

"Alkylsulfinyl" means an alkyl-SO- group wherein the alkyl group is as defined above. Preferred groups are those wherein the alkyl group is lower alkyl.

"Alkylsulfonyl" means an alkyl-SO_2-group wherein the alkyl group is as defined above. Preferred groups are those wherein the alkyl group is lower alkyl.

"Alkylthio" means an alkyl-S- group wherein the alkyl group is as defined above. Exemplary alkylthio groups include methylthio, ethylthio, i-propylthio and heptylthio.

"Aralkoxy" means an aralkyl-O- group wherein the aralkyl group is as defined herein. Exemplary aralkoxy groups include benzyloxy and 1- and 2-naphthalenemethoxy.

"Aralkoxycarbonyl" means an aralkyl-O-CO- group wherein the aralkyl group is as defined herein. An exemplary aralkoxycarbonyl group is benzyloxycarbonyl.

"Aralkyl" means an aryl-alkyl- group wherein the aryl and alkyl groups are as defined herein. Preferred aralkyls contain a lower alkyl moiety. Exemplary aralkyl groups include benzyl, 2-phenethyl and naphthalenemethyl.

"Aralkylsulfonyl" means an aralkyl-SO_2- group wherein the aralkyl group is as defined herein.

"Aralkylsulfinyl" means an aralkyl-SO- group wherein the aralkyl group is as defined herein.

"Aralkylthio" means an aralkyl-S- group wherein the aralkyl group is as defined herein. An exemplary aralkylthio group is benzylthio.

"Aroyl" means an aryl-CO- group wherein the aryl group is as defined herein. Exemplary aroyl groups include benzoyl and 1- and 2-naphthoyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system of about 6 to about 14 carbon atoms, preferably of about 6 to about 10 carbon atoms. The aryl is optionally substituted

heterocyclenyl portion of the fused arylheterocyclenyl is also optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary fused arylheterocyclenyl include 3H-indolinyl, 2(1H)quinolinonyl, 2H-1-oxoisoquinolyl, 1,2-dihydroquinolinyl, (2H)quinolinyl N-oxide, 3,4-dihydroquinolinyl, 1,2-dihydroisoquinolinyl, 3,4-dihydroisoquinolinyl, chromonyl, 3,4-dihydroisoquinoxalinyl, 4-(3H)quinazolinonyl, 4H-chromen-2yl, and the like. Preferably, 2(1H)quinolinonyl, 1,2-dihydroquinolinyl, (2H)quinolinyl N-oxide, or 4-(3H)quinazolinonyl.

"Fused arylheterocyclyl" means a fused aryl and heterocyclyl wherein the aryl and heterocyclyl groups are as defined herein. Preferred fused arylheterocyclyls are those wherein the aryl thereof is phenyl and the heterocyclyl consists of about 5 to about 6 ring atoms. A fused arylheterocyclyl may be bonded to the rest of the compound through any atom of the fused system capable of such bonding. The designation of aza, oxa or thia as a prefix before the heterocyclyl portion of the fused arylheterocyclyl means that a nitrogen, oxygen or sulphur atom respectively is present as a ring atom. The fused arylheterocyclyl group may be optionally substituted by one or more ring group substituents, wherein the "ring group substituent" is as defined herein. The nitrogen atom of a fused arylheterocyclyl may be a basic nitrogen atom. The nitrogen or sulphur atom of the heterocyclyl portion of the fused arylheterocyclyl is also optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary fused arylheterocyclyl ring systems include indolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 1H-2,3-dihydroisoindol-2-yl, 2,3-dihydrobenz[f]isoindol-2-yl, 1,2,3,4-tetrahydrobenz[g]isoquinolin-2-yl, chromanyl, isochromanonyl, 2,3-dihydrochromonyl, 1,4-benzodioxan, 1,2,3,4-tetrahydroquinoxalinyl, and the like. Preferably , 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinoxalinyl, and 1,2,3,4-tetrahydroquinolinyl.

"Aryloxy" means an aryl-O- group wherein the aryl group is as defined herein. Exemplary groups include phenoxy and 2-naphthyloxy.

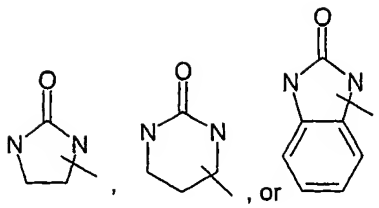
"Aryloxycarbonyl" means an aryl-O-CO- group wherein the aryl group is as defined herein. Exemplary aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl.

"Arylsulfonyl" means an aryl-SO_2- group wherein the aryl group is as defined herein.

"Arylsulfinyl" means an aryl-SO- group wherein the aryl group is as defined herein.

"Arylthio" means an aryl-S- group wherein the aryl group is as defined herein. Exemplary arylthio groups include phenylthio and naphthylthio.

"Carbamoyl" is an NH_2-CO- group.



The cyclo-imide moiety may be attached to the parent molecule through either a carbon atom or nitrogen atom of the carbamoyl moiety. An exemplary imide group is N-phthalimide.

"Diazo" means a bivalent -N=N- radical.

"Halo" means fluoro, chloro, bromo, or iodo. Preferred are fluoro, chloro and bromo, more preferably fluoro and chloro.

"Heteroaralkyl" means a heteroaryl-alkyl- group wherein the heteroaryl and alkyl groups are as defined herein. Preferred heteroaralkyls contain a lower alkyl moiety. Exemplary heteroaralkyl groups include thienylmethyl, pyridylmethyl, imidazolylmethyl and pyrazinylmethyl.

"Heteroaralkylthio" means a heteroaralkyl-S- group wherein the heteroaralkyl group is as defined herein. An exemplary heteroaralkylthio group is 3-pyridinepropanthiol.

"Heteroaralkoxy" means an heteroaralkyl-O- group wherein the heteroaralkyl group is as defined herein. An exemplary heteroaralkoxy group is 4-pyridylmethyloxy.

"Heteroaroyl" means an means an heteroaryl-CO- group wherein the heteroaryl group is as defined herein. Exemplary heteroaryl groups include thiophenoyl, nicotinoyl, pyrrol-2-ylcarbonyl and 1- and 2-naphthoyl and pyridinoyl.

"Heteroaryldiazo" means an heteroaryl-diazo- group wherein the heteroaryl and diazo groups are as defined herein.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system of about 5 to about 14 carbon atoms, preferably about 5 to about 10 carbon atoms, in which at least one of the carbon atoms in the ring system is replaced by a hetero atom, i.e., other than carbon, for example nitrogen, oxygen or sulfur. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms. The heteroaryl ring is optionally substituted by one or more "ring group substituents" which may be the same or different, and are as defined herein. The designation of aza, oxa or thia as a prefix before the heteroaryl means that a nitrogen, oxygen or sulfur atom is present, respectively, as a ring atom. A nitrogen atom of an heteroaryl may be a

designation of aza, oxa or thia as a prefix before the heteroaryl portion of the fused heteroarylcycloalkyl means that a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The fused heteroarylcycloalkyl may be optionally substituted by one or more ring group substituents, wherein the "ring group substituent" is as defined herein. The nitrogen atom of a fused heteroarylcycloalkyl may be a basic nitrogen atom. The nitrogen atom of the heteroaryl portion of the fused heteroarylcycloalkyl may also be optionally oxidized to the corresponding N-oxide. Exemplary fused heteroarylcycloalkyl include 5,6,7,8-tetrahydroquinolinyl; 5,6,7,8-tetrahydroisoquinolyl; 5,6,7,8-tetrahydroquinoxalinyl; 5,6,7,8-tetrahydroquinazolyl; 4,5,6,7-tetrahydro-1H-benzimidazolyl; 4,5,6,7-tetrahydrobenzoxazolyl; 1H-4-oxa-1,5-diazanaphthalen-2-only; 1,3-dihydroimidizole-[4,5]-pyridin-2-only; 2,3-dihydro-1,4-dinaphthoquinonyl and the like, preferably, 5,6,7,8-tetrahydroquinolinyl or 5,6,7,8-tetrahydroisoquinolyl.

"Fused heteroarylheterocyclenyl" means a fused heteroaryl and heterocyclenyl wherein the heteraryl and heterocyclenyl groups are as defined herein. Preferred fused heteroarylheterocyclenyls are those wherein the heteroaryl thereof consists of about 5 to about 6 ring atoms and the heterocyclenyl consists of about 5 to about 6 ring atoms. A fused heteroarylheterocyclenyl may be bonded to the rest of the compound through any atom of the fused system capable of such bonding. The designation of aza, oxa or thia as a prefix before the heteroaryl or heterocyclenyl portion of the fused heteroarylheterocyclenyl means that a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The fused heteroarylheterocyclenyl may be optionally substituted by one or more ring group substituent, wherein the "ring group substituent" is as defined herein. The nitrogen atom of a fused heteroarylazaheterocyclenyl may be a basic nitrogen atom. The nitrogen or sulphur atom of the heteroaryl or heterocyclenyl portion of the fused heteroarylheterocyclenyl may also be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary fused heteroarylheterocyclenyl groups include 7,8-dihydro[1,7]naphthyridinyl; 1,2-dihydro[2,7]naphthyridinyl; 6,7-dihydro-3H-imidazo[4,5-c]pyridyl; 1,2-dihydro-1,5-naphthyridinyl; 1,2-dihydro-1,6-naphthyridinyl; 1,2-dihydro-1,7-naphthyridinyl; 1,2-dihydro-1,8-naphthyridinyl; 1,2-dihydro-2,6-naphthyridinyl, and the like.

"Fused heteroarylheterocyclyl" means a fused heteroaryl and heterocyclyl wherein the heteroaryl and heterocyclyl groups are as defined herein. Preferred fused

double bond or carbon-nitrogen double bond. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms. The designation of aza, oxa or thia as a prefix before the heterocyclenyl means that a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The heterocyclenyl may be optionally substituted by one or more ring group substituents, wherein the "ring group substituent" is as defined herein. The nitrogen atom of an heterocyclenyl may be a basic nitrogen atom. The nitrogen or sulphur atom of the heterocyclenyl is also optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary monocyclic azaheterocyclenyl groups include 1,2,3,4- tetrahydrohydropyridine, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetrahydropyridine, 1,4,5,6-tetrahydropyrimidine, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, and the like. Exemplary oxaheterocyclenyl groups include 3,4-dihydro-2H-pyran, dihydrofuryl, and fluorodihydrofuryl An exemplary multicyclic oxaheterocyclenyl group is 7-oxabicyclo[2.2.1]heptenyl. Exemplary monocyclic thiaheterocycleny rings include dihydrothiophenyl and dihydrothiopyranyl.

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system of about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms, in which at least one of the carbon atoms in the ring system is replaced by a hetero atom, for example nitrogen, oxygen or sulfur. Preferred ring sizes of rings of the ring system include about 5 to about 6 ring atoms. The designation of aza, oxa or thia as a prefix before the heterocyclyl means that a nitrogen, oxygen or sulfur atom is present respectively as a ring atom. The heterocyclyl may be optionally substituted by one or more "ring group substituents" which may be the same or different, and are as defined herein. The nitrogen atom of an heterocyclyl may be a basic nitrogen atom. The nitrogen or sulphur atom of the heterocyclyl is also optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Exemplary monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,3-dioxolanyl, 1,4-dioxanyl, tetrahydrofuryl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like. Exemplary multicyclic heterocyclyl rings include 1,4 diazabicyclo-[2.2.2]octane and 1,2-cyclohexanedicarboxylic acid anhydride.

"Ring group substituent" includes hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroaralkyl, hydroxy, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl,

"Treating" means the partial or complete relieving or preventing of one or more physiological or biochemical parameters associated with ABC-1 activity.

The term "modulate" refers to the ability of a compound to either directly (by binding to the receptor as a ligand) or indirectly (as a precursor for a ligand or an inducer which promotes production of a ligand from a precursor) induce expression of gene(s) maintained under hormone control, or to repress expression of gene (s) maintained under such control.

The term "obesity" refers generally to individuals who are at least about 20-30% over the average weight for the person's age, sex and height. Technically, "obese" is defined, for males, as individuals whose body mass index is greater than 27.3 kg/m^2. Those skilled in the art readily recognize that the invention method is not limited to those who fall within the above criteria. Indeed, the invention method can also be advantageously practiced by individuals who fall outside of these traditional criteria, for example by those who are prone to obesity.

The phrase "amount effective to lower blood glucose levels" refers to levels of a compound sufficient to provide circulating concentrations high enough to accomplish the desired effect. Such a concentration typically falls in the range of about 10nM up to 2μM, with concentrations in the range of about 100nm up to about 500nM being preferred.

The phrase "amount effective to lower triclyceride levels" refers to levels of a compound sufficient to provide circulating concentrations high enough to accomplish the desired effect. Such a concentration typically falls in the range of about 10nM up to 2μM; with concentrations in the range of about 100nm up to about 500nM being preferred.

Preferred Embodiments

Preferred embodiments according to the invention include the method for modulating ABC-1 gene expression comprising contacting a PPAR receptor with a PPAR mediator.

Another preferred embodiment according to the invention includes the method for modulating ABC-1 gene expression comprising contacting a PPAR receptor with a PPAR-α mediator.

Another preferred embodiment according to the invention includes the method for modulating ABC-1 gene expression comprising contacting a PPAR receptor with a PPAR-δ mediator.

comprising administering to a patient in need of such treatment, a pharmaceutically effective amount of a compound of Formula I.

Another preferred embodiment according to the invention includes the method of treating a physiological condition in a patient associated with ABC-1 gene expression comprising administering to a patient in need of such treatment, a pharmaceutically effective amount of compound selected from the group consisting of Nafenopn , UF-5, ETYA, GW2331, 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2, clofibric, linoleic acid, BRL-49653, fenofibrate, WR-1339, Pioglitazone, Ciglitazone, Englitazone, Troglitazone, LY-171883, AD 5075, 5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, WAY-120,744, and Darglitazone and their pharmaceutically acceptable salts.

Another preferred embodiment according to the invention includes the method of treating a disease associated with deficient levels of ABC1 gene expression, selected from the group consisting of atherosclerosis, fish-eye disease, familial HDL deficiencies (FHD), Tangier disease, LCAT deficiency, cholesterol efflux, malaria and diabetes, comprising administering to a patient in need of such treatment, a pharmaceutically effective amount of a PPAR agonist.

Another preferred embodiment according to the invention includes the method of treating a disease associated with deficient levels of ABC1 gene expression, selected from the group consisting of atherosclerosis, fish-eye disease, familial HDL deficiencies (FHD), Tangier disease, LCAT deficiency, cholesterol efflux, malaria and diabetes, comprising administering to a patient in need of such treatment, a pharmaceutically effective amount of a PPAR agonist of formula (I).

An embodiment according to the invention is the use of compounds of Formula I (and their pharmaceutical compositions) as binders for PPAR receptors.

More particularly, the use of compounds of Formula I that bind to the PPAR-α receptor,

compounds of Formula I that bind to the PPAR-δ receptor,

compounds of Formula I that bind to the PPAR-γ receptor,

compounds of Formula I that bind to the PPAR-α and the PPAR-γ receptor,

compounds of Formula I that bind to the PPAR-α and the PPAR-δ receptor,

compounds of Formula I that bind to the PPAR-γ and the PPAR-δ receptor,

compounds of Formula I that act as PPAR receptor agonists,

compounds of Formula I that act as PPAR-α receptor agonists,

beta cell function, insulin secreting tumors and /or autoimmune hypoglycemia due to autoantibodies to insulin, autoantibodies to the insulin receptor, or autoantibodies that are stimulatory to pancreatic beta cells), macrophage differentiation which leads to the formation of atherosclerotic plaques, inflammatory response, carcinogenesis, hyperplasia, adipocyte gene expression, adipocyte differentiation, reduction in the pancreatic β-cell mass, insulin secretion, tissue sensitivity to insulin, liposarcoma cell growth, chronic anovulation, hyperandrogenism, progesterone production, steroidogenesis, redox potential and oxidative stress in cells, nitric oxide synthase (NOS) production, increased gamma glutamyl transpeptidase, catalase, plasma triglycerides, HDL and LDL cholesterol levels and the like.

Another embodiment according to the invention is directed to a method of treating a disease state in a patient with a pharmaceutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein the disease is associated with a physiological detrimental blood level of insulin, glucose, free fatty acids (FFA), or triglycerides.

An embodiment according to the invention is directed to treating a patient suffering from a physiological disorder associated with physiologically detrimental levels of triglycerides in the blood, by administering to the patient a pharmaceutically effective amount of the compound, or of a pharmaceutically acceptable salt thereof.

An embodiment according to the invention is the use of compounds of Formula I and their pharmaceutical compositions as anti-diabetic, anti-lipidemic, anti-hypertensive or anti-arteriosclerotic agents, or in the treatment of obesity.

Another embodiment according to the invention is directed to a method of treating hyperglycemia in a patient, by administering to the patient a pharmaceutically effective amount to lower blood glucose levels of a compound of Formula I, or a pharmaceutically acceptable salt thereof. Preferably, the form of hyperglycemia treated in accordance with this invention is Type II diabetes.

Another embodiment according to the invention is directed to a method of reducing triglyceride levels in a patient, comprising administering to the patient a therapeutically effective amount (to lower triglyceride levels) of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

Another embodiment according to the invention is directed to treating climacteric comprising administering to the patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

Another embodiment according to the invention is directed to treating inflammatory diseases comprising administering to the patient a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

Another aspect of the invention is to provide a novel pharmaceutical composition which is effective, in and of itself, for utilization in a beneficial combination therapy because it includes a plurality of active ingredients which may be utilized in accordance with the invention.

In another aspect, the present invention provides a method for treating a disease state in a patient, wherein the disease is associated with a physiological detrimental level of insulin, glucose, free fatty acids (FFA), or triglycerides, in the blood, comprising administering to the patient a therapeutically effective amount of a compound of Formula I, and also administering a therapeutically effective amount of an additional hypoglycemic agent.

In another aspect, the present invention provides a method for treating a disease state in a patient, wherein the disease is associated with a physiological detrimental level of insulin, glucose, free fatty acids (FFA), or triglycerides, in the blood, comprising administering to the patient a therapeutically effective amount of a compound of Formula I, and also administering a therapeutically effective amount of a biguanidine compound.

In another aspect, the present invention provides a method for treating a disease state in a patient, wherein the disease is associated with a physiological detrimental level of insulin, glucose, free fatty acids (FFA), or triglycerides, in the blood, comprising administering to the patient a therapeutically effective amount of a compound of Formula I, and also administering a therapeutically effective amount of metformin.

The invention also provides kits or single packages combining two or more active ingredients useful in treating the disease. A kit may provide (alone or in combination with a pharmaceutically acceptable diluent or carrier), a compound of Formula (I) and an additional hypoglycaemic agent (alone or in combination with diluent or carrier).

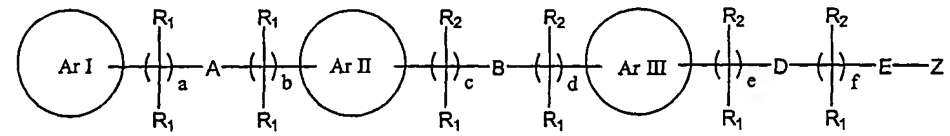
There are many known hypoglycemic agents in the art, for example, insulin; biguanidines, such as metformin and buformin; sulfonylureas, such as acetohexamide,

tablet or capsule, or each agent administered in separate oral dosage formulations. Where separate dosage formulations are used, the compound of Formula I and one or more additional hypoglycemic agents can be administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e., sequentially.

For example, the compound of Formula I may be administered in combination with one or more of the following additional hypoglycemic agents: insulin; biguanidines such as metformin or buformin; sulfonylureas such as acetohexamide, chloropropamide, tolazamide, tolbutamide, glyburide, glypizide or glyclazide; thiazolidinediones such as troglitazone; α-glycosidase inhibitors such as acarbose or miglatol; or B_3 adrenorecptor agonists such as CL-316, 243.

The compound of Formula I is preferably administered with a biguanidine, in particular, metformin.

The compounds of Formula I contain at least three aromatic or hetero-aromatic rings, which may be designated as shown in Formula II below, and for which their substitution pattern along the chain with respect to each other also is shown below.

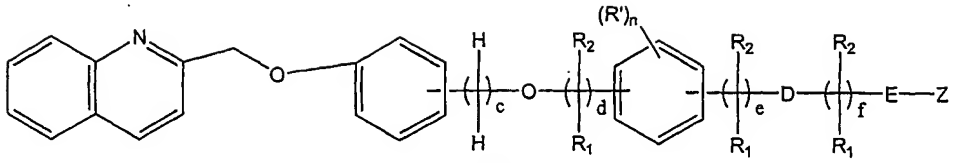


(II)

A preferred aspect of the compounds of Formula II, is a compound wherein 

is selected from quinolinyl, benzothiophenyl, benzoimidazolyl, quinazolinyl, benzothiazolyl, quinoxalinyl, naphthyl, pyridyl,1H-indazolyl, 1,2,3,4-tetrahydroquinolinyl, benzofuranyl, thienyl, or indolyl, and one end of the linker, Linker I, is attached to 

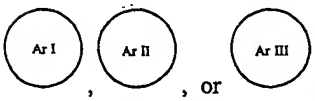
preferably at the 2-position of the ring moiety.



(V)

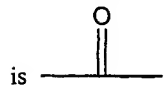
where R_1, R_2, c, d, e, f, n, D, E and Z are as defined above, c + d = 1-3, and R' is a ring group substituent.

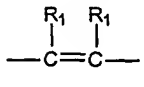
A further preferred aspect of the compound of Formula I is a compound wherein



, , or is independently phenyl, naphthyl, phenyl, naphthyl, 1,2-dihydronaphthylenyl, indenyl, 1,4-naphthoquinonyl, 1,2,3,4-tetrahydronaphthylenyl, 1,4-tetramethyl-2,3-dihydronaphthalenyl, 2,3-dihydro-1,4-naphthoquinonyl, α-tetralonyl, 3H-indolinyl, 2(1H)quinolinonyl, 2H-1-oxoisoquinolyl, 1,2-dihydroquinolinyl, 3,4-dihydroquinolinyl, 1,2-dihydroisoquinolinyl, 3,4-dihydroisoquinolinyl, chromonyl, 3,4-dihydroisoquinoxalinyl, 4-quinazolinonyl, 4H-chromen-2yl, indolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 1H-2,3-dihydroisoindol-2-yl, 2,3-dihydrobenz[f]isoindol-2-yl, 1,2,3,4-tetrahydrobenz[g]isoquinolin-2-yl, chromanyl, isochromanonyl, 2,3-dihydrochromonyl, 1,4-benzodioxan, 1,2,3,4-tetrahydroquinoxalinyl, quinolinyl, indazolyl, indolyl, quinazolinyl, pyridyl, pyrimidinyl, furyl, benzothiazol, quinoxalinyl, benzimidazolyl, benzothienyl, or isoquinolinyl, 5,6-dihydroquinolyl, 5,6-dihydroisoquinolyl, 5,6-dihydroquinoxalinyl, 5,6-dihydroquinazolinyl, 4,5-dihydro-1H-benzimidazolyl, 4,5-dihydrobenzoxazolyl, 1,4-naphthoquinolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolyl, 5,6,7,8-tetrahydroquinoxalinyl, 5,6,7,8-tetrahydroquinazolyl, 4,5,6,7-tetrahydro-1H-benzimidazolyl, 4,5,6,7-tetrahydrobenzoxazolyl, 1H-4-oxa-1,5-diazanaphthalen-2-onyl, 1,3-dihydroimidizole-[4,5]-pyridin-2-onyl, 2,3-dihydro-1,4-dinaphthoquinonyl, 7,8-dihydro[1,7]naphthyridinyl, 1,2-dihydro[2,7]naphthyridinyl, 6,7-dihydro-3H-imidazo[4,5-c]pyridyl, 1,2-dihydro-1,5-naphthyridinyl, 1,2-dihydro-1,6-naphthyridinyl, 1,2-dihydro-1,7-naphthyridinyl, 1,2-dihydro-1,8-naphthyridinyl, 1,2-dihydro-2,6-naphthyridinyl, 2,3-dihydro-1H pyrrol[3,4-b]quinolin-2-yl, 1,2,3,4-tetrahydrobenz

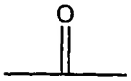
A further preferred aspect of the compound of Formula I is the compound wherein a=1, A is O, and b=0.

A further preferred aspect of the compound of Formula I is a compound wherein a=0, A is  , and b=0.

A further preferred aspect of compounds of Formula I is a compound wherein a=0, A is  , and b=0.

A further preferred aspect of compounds of Formula I is a compound wherein c=0, and d=1.

A further preferred aspect of compounds of Formula I is a compound wherein c=0, B is O, and d=1.

A further preferred aspect of compounds of Formula I is a compound wherein c=0, B is  , d=1, R_1 is hydrogen, R_2 is $-(CH_2)_q - X$, q is 1, is heteroaryl.

A further preferred aspect of compounds of Formula I is a compound wherein a+b=0-2.

A further preferred aspect of compounds of Formula I is a compound wherein a+b=1.

A further preferred aspect of compounds of Formula I is a compound wherein c=1, d=0.

A further preferred aspect of compounds of Formula I is a compound wherein B is a chemical bond.

A further preferred aspect of compounds of Formula I is a compound wherein c=1, d=0, and B is a chemical bond.

A further preferred aspect of compounds of Formula I is a compound wherein c=0, d=0, and B is a chemical bond.

A further preferred aspect of compounds of Formula I is a compound wherein e+f=0-4.

A further preferred aspect of compounds of Formula I is a compound wherein e+f=3.

A further preferred aspect of compounds of Formula I is a compound wherein e+f=1.

A further preferred aspect of compounds of Formula I is a compound wherein e+f=1, and D and E are chemical bonds.

A further preferred aspect of compounds of Formula I is a compound wherein e=0 and D is a chemical bond.

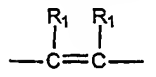
A further preferred aspect of compounds of Formula I is a compound wherein e=0, D is a chemical bond, and E is a chemical bond.

A further preferred aspect of compounds of Formula I is a compound wherein e=1 and geminal R_1 and R_2 taken together with the carbon atom to which the geminal R_1 and R_2 are attached form carbonyl.

A further preferred aspect of compounds of Formula I is a compound wherein e=1 and geminal R_1 and R_2 taken together with the carbon atom to which the geminal R_1 and R_2 are attached form cycloalkylene.

A further preferred aspect of compounds of Formula I is a compound wherein two R_1 taken together with the carbons atom to which the R_1 are linked form cycloalkylene.

A further preferred aspect of compounds of Formula I is a compound wherein two vicinal R_1 taken together with the carbons atom to which the vicinal R_1 are linked form



A further preferred aspect of compounds of Formula I is a compound wherein geminal R_1 and R_1 taken together with the carbon atom to which the geminal R_1 and R_1 are attached to form carbonyl.

A further preferred aspect of the compound of Formula I is a compound wherein R_1 is carboxyl.

A further preferred aspect of the compound of Formula I is a compound wherein R_1 is alkoxycarbonyl.

A further preferred aspect of compounds of Formula I is a compound wherein e=2, and geminal R_1 and R_2 taken together with the carbon atom to which the geminal R_1 and R_2 are attached independently form cycloalkylene or carbonyl.

A further preferred aspect of compounds of Formula I is a compound wherein e=2, R_1 and R_2 are independently alkyl, or geminal R_1 and R_2 taken together with the carbon atom to which the geminal R_1 and R_2 are attached form carbonyl.

A further preferred aspect of compounds of Formula I is a compound wherein f=2, R_1 is hydrogen, and R_2 is independently hydrogen or alkoxy.

A further preferred aspect of compounds of Formula I is a compound wherein f=3, R_1 is hydrogen, and R_2 is independently hydrogen or alkoxy.

A further preferred aspect of compounds of Formula I is a compound wherein f=1, R_1 is halogen, and R_2 is halogen.

A further preferred aspect of compounds of Formula I is a compound wherein f=2, R_1 is halogen, and R_2 is independently hydrogen or halogen.

A further preferred aspect of compounds of Formula I is a compound wherein f=3, R_1 is halogen, and R_2 is independently hydrogen or halogen.

A further preferred aspect of compounds of Formula I is a compound wherein f=1, R_1 is fluoro, and R_2 is fluoro.

A further preferred aspect of compounds of Formula I is a compound wherein f=2, R_1 is fluoro, and R_2 is independently hydrogen or fluoro.

A further preferred aspect of compounds of Formula I is a compound wherein f=3, R_1 is fluoro, and R_2 is independently hydrogen or fluoro.

A further preferred aspect of compounds of Formula I is a compound wherein f=1, R_1 is alkyl, and R_2 is alkyl.

A further preferred aspect of compounds of Formula I is a compound wherein f=2, R_1 is alkyl, and R_2 is independently hydrogen or alkyl.

A further preferred aspect of compounds of Formula I is a compound wherein f=3, R_1 is alkyl, and R_2 is independently hydrogen or alkyl.

A further preferred aspect of compounds of Formula I is a compound wherein f=1, R_1 is aralkyl, and R_2 is alkyl.

A further preferred aspect of compounds of Formula I is a compound wherein f=1, R_1 is aralkyl, and R_2 is aralkyl.

A further preferred aspect of compounds of Formula I is a compound wherein f=1, R_1 is aralkyl, and R_2 is aryl.

A further preferred aspect of compounds of Formula I is a compound wherein f=1, R_1 is aralkyl, and R_2 is heteroaryl.

A further preferred aspect of compounds of Formula I is a compound wherein Z is R_3O_2SHN-.

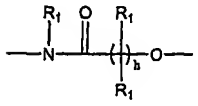
A further preferred aspect of compounds of Formula I is a compound wherein Z is $(R_3)_2NCO$-, and R_3 is hydrogen or alkyl.

A further preferred aspect of compounds of Formula I is a compound wherein Z is R_3O- and R_3 is hydrogen, alkyl, or aryl.

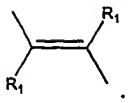
A further preferred aspect of compounds of Formula I is a compound wherein f=1, R_1 is hydrogen, R_2 is -$(CH2)_q$-X, q=1, and X is alkyl.

A further preferred aspect of compounds of Formula I is a compound wherein R_1 is H, alkyl, or aryl.

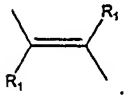
A further preferred aspect of compounds of Formula I is a compound wherein A is



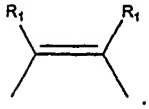
A further preferred aspect of compounds of Formula I is a compound wherein A is



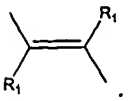
A further preferred aspect of compounds of Formula I is a compound wherein B is

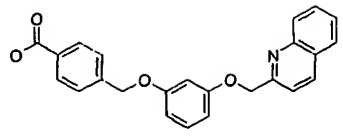


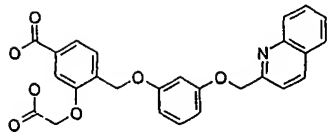
A further preferred aspect of compounds of Formula I is a compound wherein B is

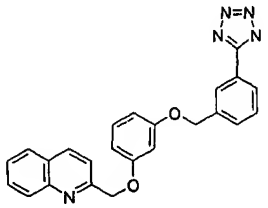


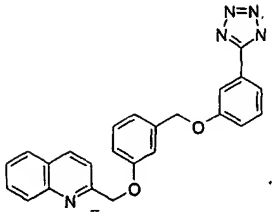
A further preferred aspect of compounds of Formula I is a compound wherein D is

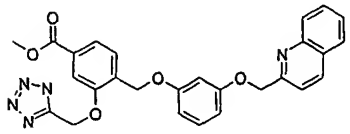


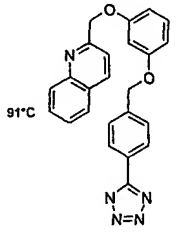
190-192°C  ;

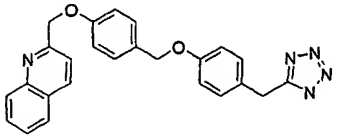
226-228°C  ;

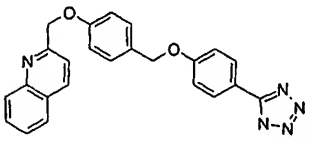
115°C (dec)  ;

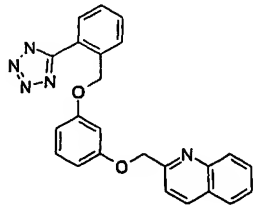
169-172°C  ;

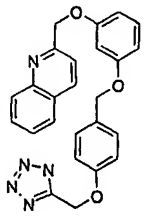
159-162°C  ;

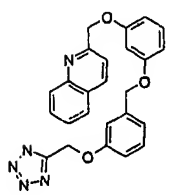
91°C  ;

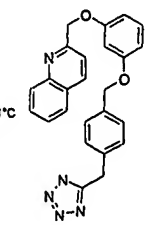
179-181°C  ;

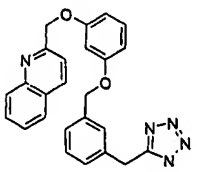
210-213°C  ;

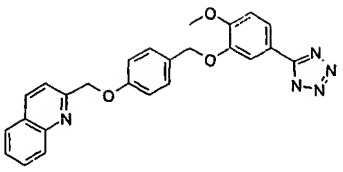
166-170°C  ;

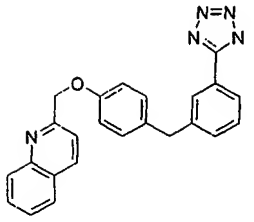
154-156°C  ;

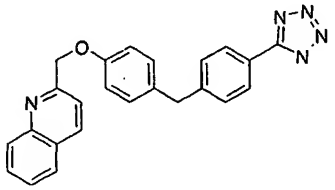
135-138°C  ;

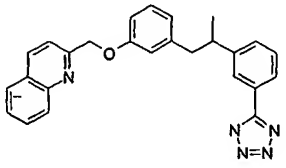
149-151°C  ;

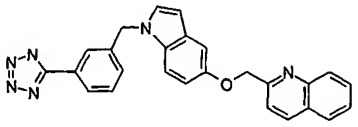
161-164°C  ;

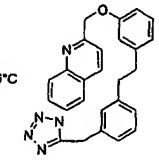
210-213°C  ;

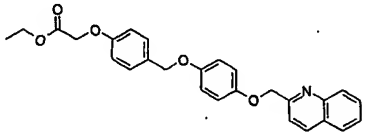
186-189°C  ;

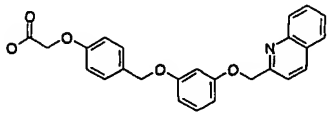
206-209°C  ;

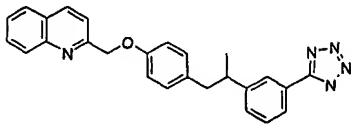
83-86°C  ;

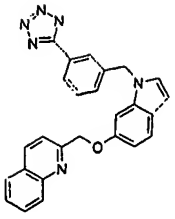
173-176°C  ;

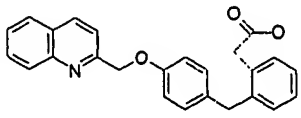
53-56°C  ;

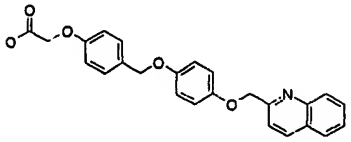
121-126°C  ;

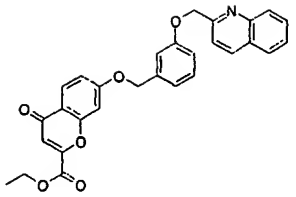
164°C (dec)  ;

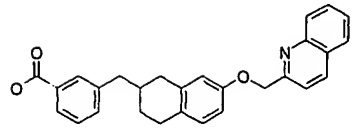
170-173°C  ;

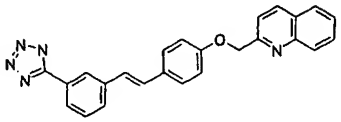
220-221°C  ;

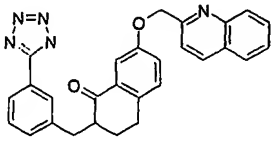
183-186°C  ;

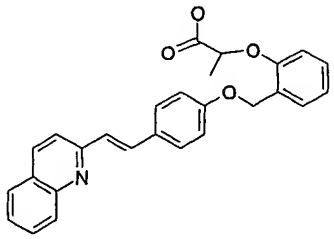
128°C (dec)  ;

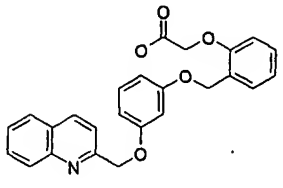
123-124°C  ;

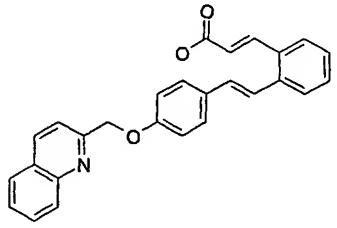
156-158°C  ;

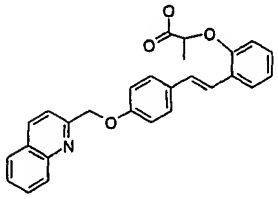
50-51°C  ;

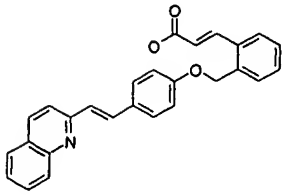
187-188°C  ;

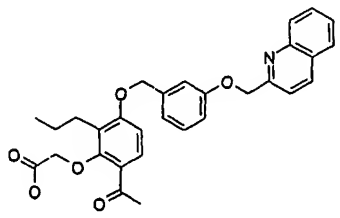
201-203°C  ;

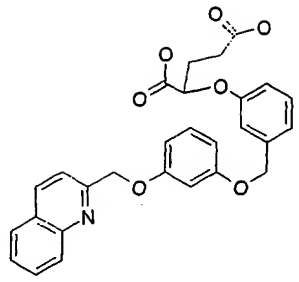
169-172°C  ;

195-197°C  ;

96-97°C  ;

206-209°C  ;

153-158°C  ;

129-130°C 

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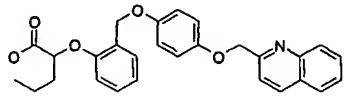
85-92°C 

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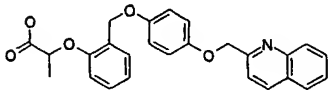
161-164°C 

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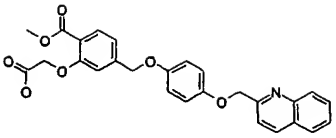
149-151°C 

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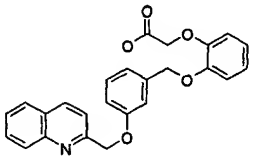
153-155°C 

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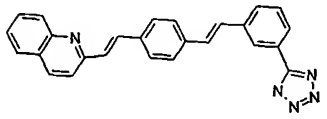
165-169°C 

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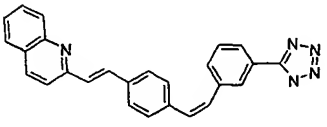
189-193°C 

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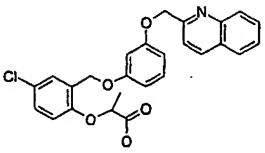
169-171°C 

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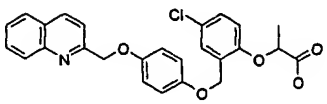
196-199°C 

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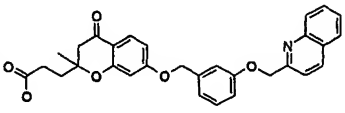
152-154°C 

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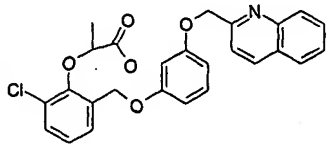
156-159°C 

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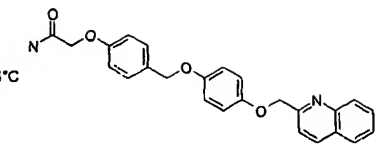
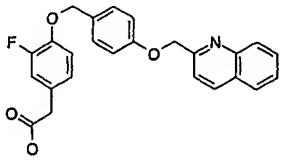
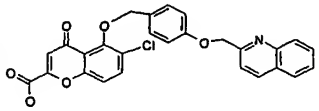
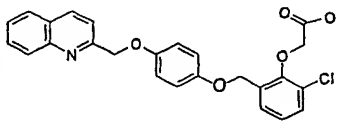
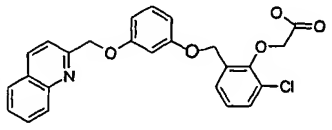
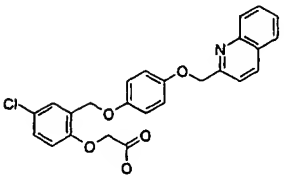
182-184°C  ;

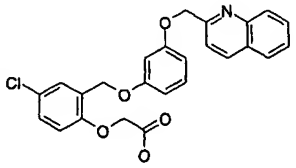
173-4°C (dec)  ;

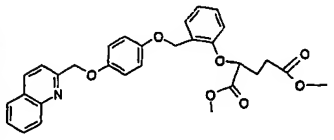
173-5°C (dec)  ;

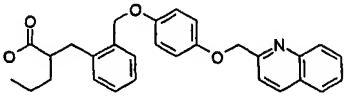
188-191°C  ;

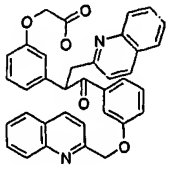
179-181°C  ;

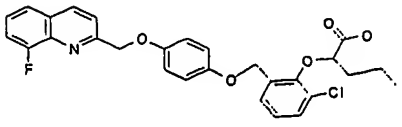
177-180°C  ;

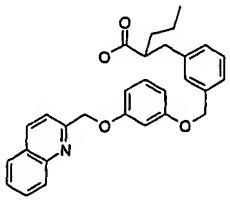
189-191°C  ;

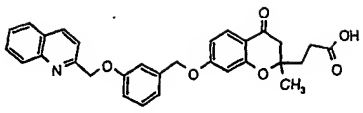
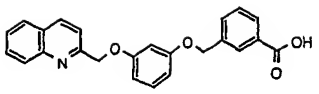
oil; CHN calc. C30H29NO7+0.5 H2O: C 68.69, H 5.76, N 2.67; found C 68.68, H 5.71, N 2.86  ;

128-132°C  ;

104-106°C  ;

173-177°C  ;

CHN calc. C29H29NO + 0.75 H2O: C 74.26, H 6.55, N 2.99; found C 73.97, H 6.31, N 2.89  ;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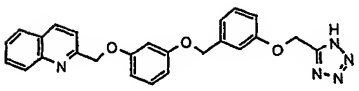
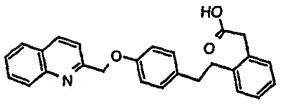
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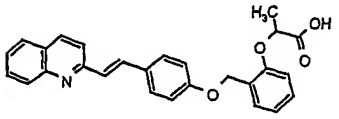
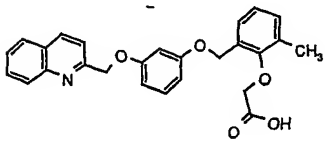
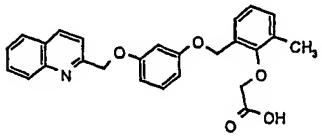
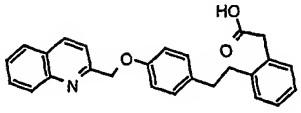


; and

A more preferred compound according to the invention is selected from the group consisting of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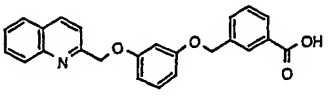
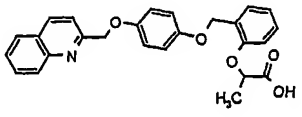
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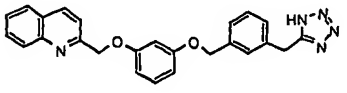
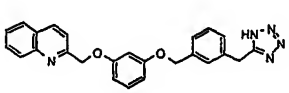
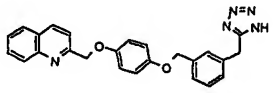

and

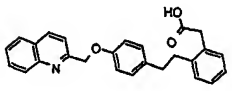
A preferred compound according to the invention having PPARα and PPARγ activity is selected from the group consisting of

A preferred compound according to the invention that is selective for PPARδ and PPARγ is selected from the group consisting of:

; and

A preferred compound according to the invention that is selective for PPARα and PPARδ is selected from the group consisting of: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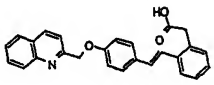
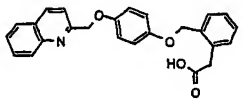
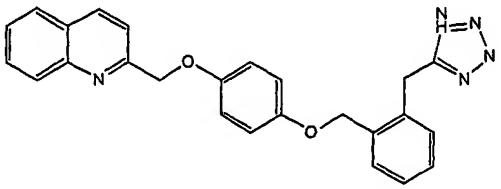

; and


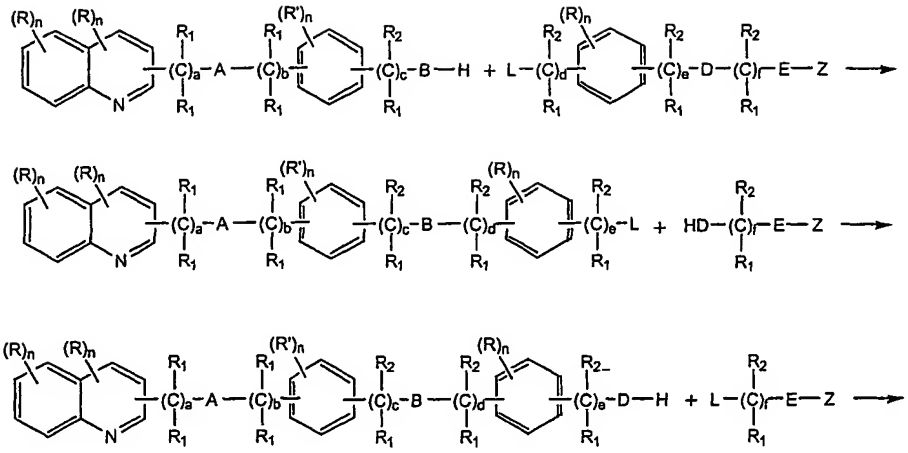
A more preferred compound of the invention having PPARγ activity has the formula VI:



(VI).

This invention also encompasses all combinations of preferred aspects of the invention noted herein.

Compounds useful according to this invention can be prepared in segments as is common to a long chain molecule. Thus it is convenient to synthesize these molecules by employing condensation reactions at the A, B and D sites of the molecule. Compounds of Formula I can be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature. Thus, compounds of Formula I are preparable by art recognized procedures from known compounds or readily preparable



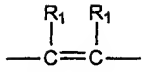
wherein:

R, R', R_1, R_2, a, b, c, d, e, f, n, A, and D are as defined above; B is O, NR_4 or S; E is a chemical bond; Z is -CN, $-COOR_3$ or tetrazol, and L is a leaving group, such as halo, tosylate, or mesylate. Where B is O or S, any base normally employed to deprotonate an alcohol or thiol may be used, such as sodium hydride, sodium hydroxide, triethylamine, sodium bicarbonate or diisopropyl/ethylamine.

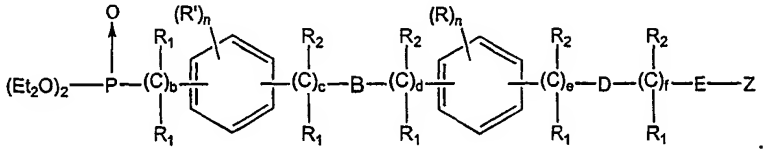
Reaction temperatures are in the range of about room temperature to reflux and reaction times vary from about 2 to about 96 hours. The reactions are usually carried out in a solvent that will dissolve both reactants and is inert to both as well. Solvents include, but are not limited to, diethyl ether, tetrahydrofuran, N,N-dimethylformamide, dimethylsulfoxide, dioxane and the like.

In the case where B is SO or SO_2 then treatment of the thio compound with m-chlorobenzoic acid or sodium periodate results in the sulfinyl compound. Preparation of the sulfonyl compound may be accomplished by known procedures such as dissolving the sulfinyl compound in acetic acid and treating with 30% H_2O_2.

Those compounds where B is



are prepared by reacting the appropriate aldehyde or ketone with a substituted Wittig reagent of the formula



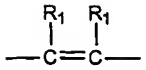
Subsequent condensation results in formation of the double bond. The Wittig reagent is prepared by known art recognized procedure such as reaction of triphenyl phosphine or diethylphosphone, with a suitable substituted alkyl/aryl bromide followed by treatment with a strong organometallic base such as n-BuLi or NaOH, which results in the desired ylide. Conventional Wittig reaction conditions may be used in accordance with standard practice. For examples, see Bestmann and Vostrowsky, Top. Curr. Chem. 109, 85-164 (1983), and Pommer and Thieme, Top. Curr. Chem. 109, 165-188 (1983).

There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved.

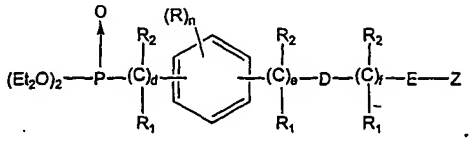
Of course, this Wittig condensation may also take place when the Wittig reagent is formed on Ring I portion of the molecule, which is then condensed with the aldehyde from the Ring II portion.

Those compounds where A is a chemical bond may be prepared by known coupling methods, for example, the reaction of an appropriate alkyl halide with an appropriate organometallic reagent such as a lithium organocopper reagent (See Posner, Org. React. 22, 235-400 (1975), Normant, Synthesis 63-80 (1972), Posner, "An introduction to Synthesis Using Organocopper Reagents" p. 68-81, Wiley, New York, 1980); coupling of an appropriate lithium organocopper reagent, or Grignard reagent, with a suitable ester of sulfuric or sulfonic acid (see "An introduction to Synthesis Using Organocopper Reagents" p. 68-81, Wiley, New York, 1980, Kharasch and Reinmuth "Grignard Reactions of Non Metallic Substances", pp1277-1286,

Those compounds where B is



are prepared by reacting the appropriate aldehyde or ketone with a substituted Wittig reagent of the formula



Condensation results in formation of the double bond. The Wittig reagent is prepared by known art recognized procedure, such as reaction of triphenyl phosphine or diethylphosphone, with a suitable substituted alkyl/aryl bromide followed by treatment with a strong organometallic base such as n-BuLi or NaOH results in the desired ylide. Conventional Wittig reaction conditions may be used in accordance with standard practice, for examples see Bestmann and Vostrowsky, Top. Curr. Chem. 109, 85-164 (1983), and Pommer and Thieme, Top. Curr. Chem. 109, 165-188 (1983).

There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or on the reagents involved.

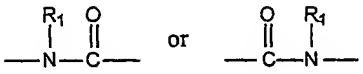
Of course this Wittig condensation may also take place when the Wittig reagent is formed on Ring II portion of the molecule which is then condensed with the aldehyde from the Ring III portion.

Those compounds where B or A is a chemical bond may be prepared by known coupling methods, for example, the reaction of an appropriate alkyl halide with an appropriate organometallic reagent such as a lithium organocopper reagent (See Posner, Org. React. 22, 235-400 (1975), Normant, Synthesis 63-80 (1972), Posner, "An introduction to Synthesis Using Organocopper Reagents" p. 68-81, Wiley, New York, 1980); coupling of an appropriate lithium organocopper reagent, or Grignard reagent, with a suitable ester of sulfuric or sulfonic acid (see "An introduction to Synthesis Using Organocopper Reagents" p. 68-81, Wiley, New York,

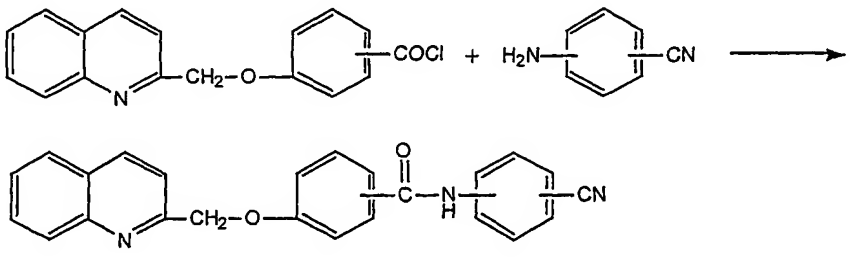
Alkenes", vol. 2, p. 175-214, Interscience, NY, 1970; and Rylander "Catalytic Hydrogenation over Platinum Metals", p. 59-120, Academic Press, NY, 1967.

The tetrazole may be formed from the nitrite at various stages of the synthesis by treatment with hydrazoic acid formed in situ from sodium azide and an acid.

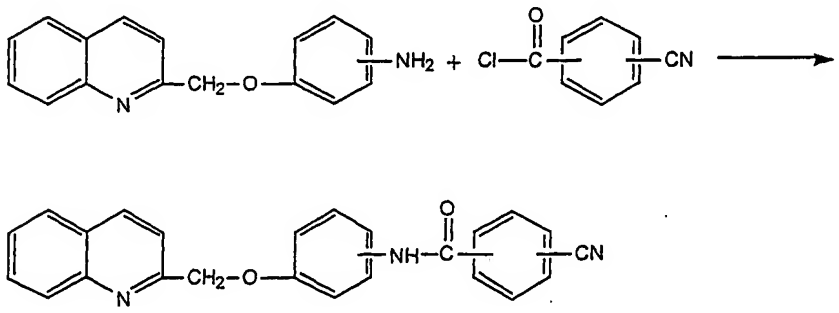
When B is



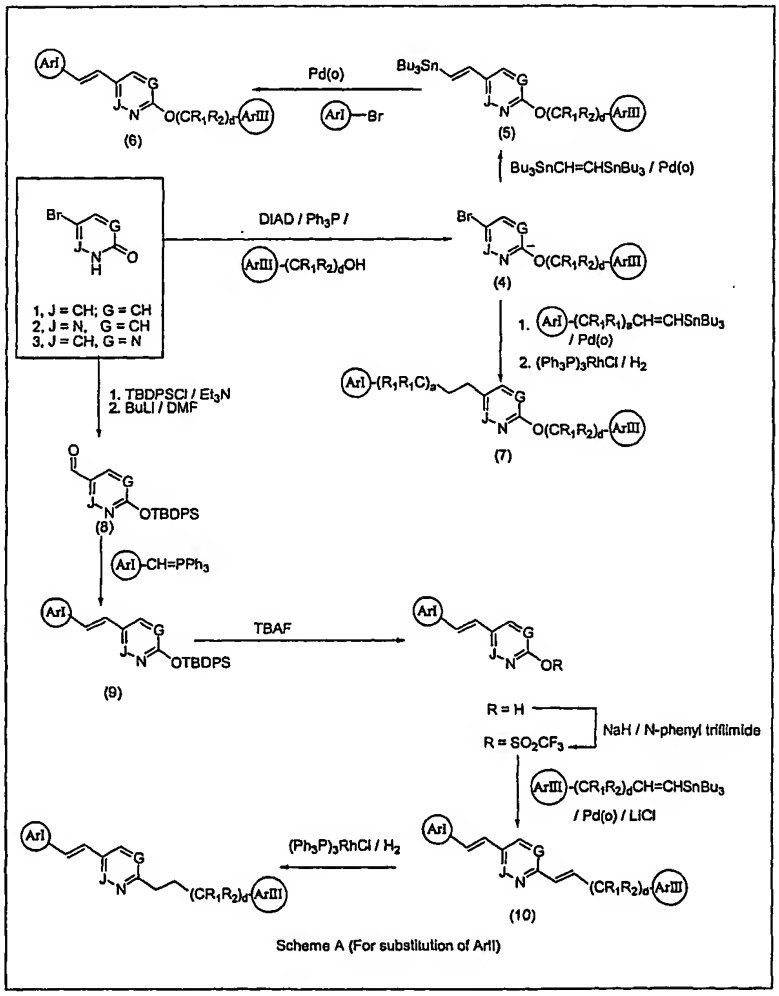
then condensation of the acid halide with the appropriate aniline will give the desired compound as shown below in the following scheme.



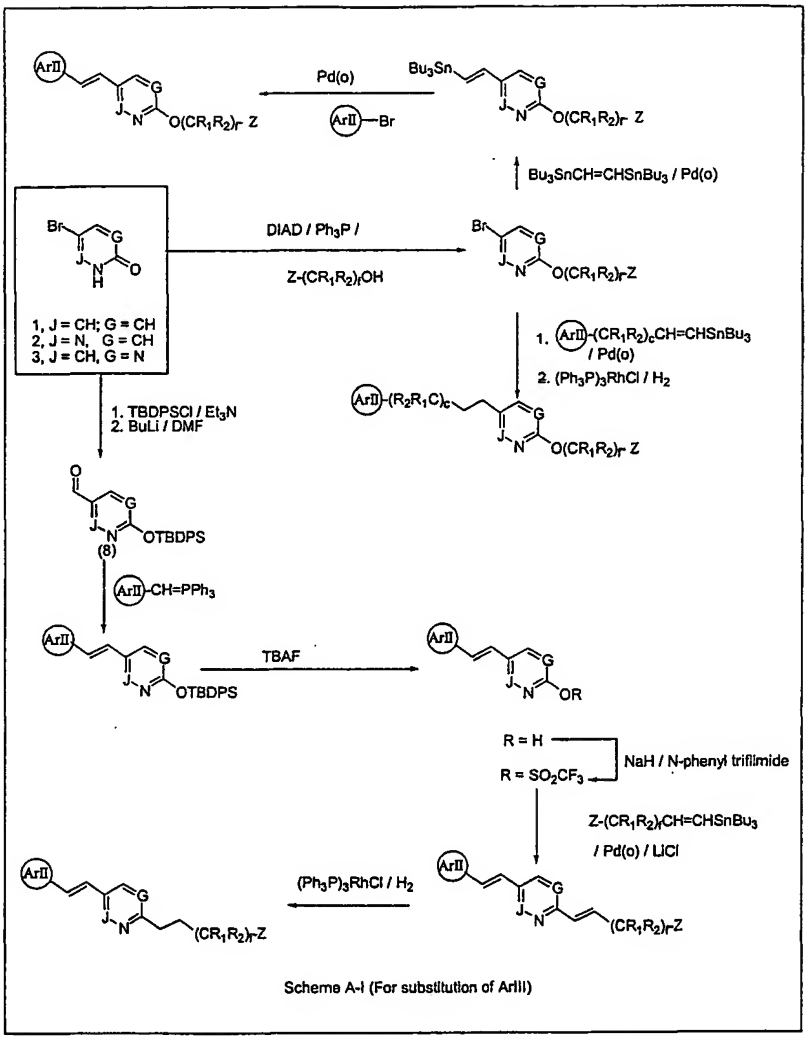
or



Mitsunobu's conditions provides the corresponding bromo-substituted heterocyclic ethers (4) (for typical procedures see Mitsunobu. O., Synthesis, 1981, 1).

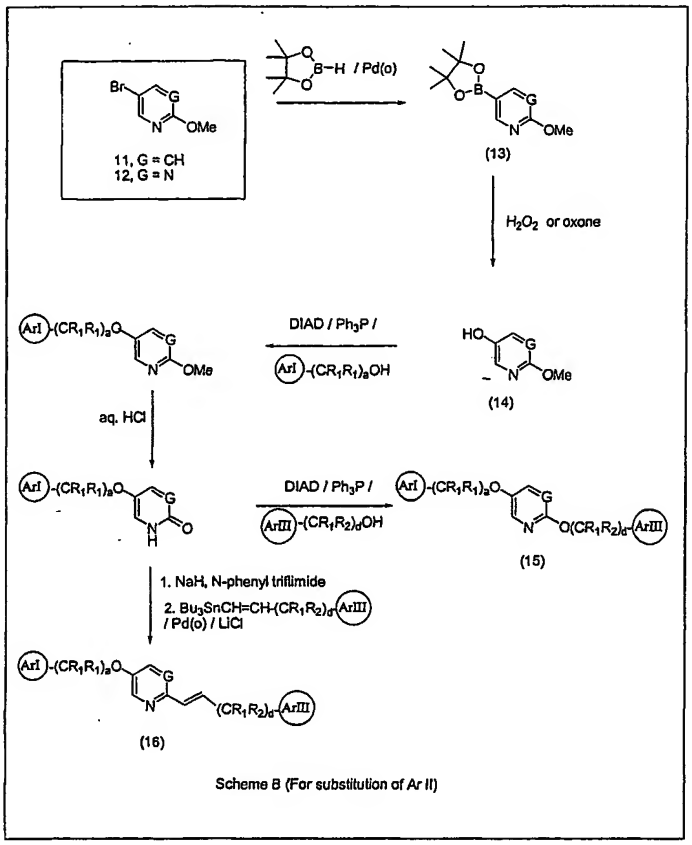


These heterocyclic bromides can be further functionalized in a number of ways. For example, coupling with a vinyl stannane can be effected under palladium (o) catalysis to provide systems with an alkenyl side chain (5 and 6). The choice of catalyst and reaction temperature depends on the substrate employed but is most commonly

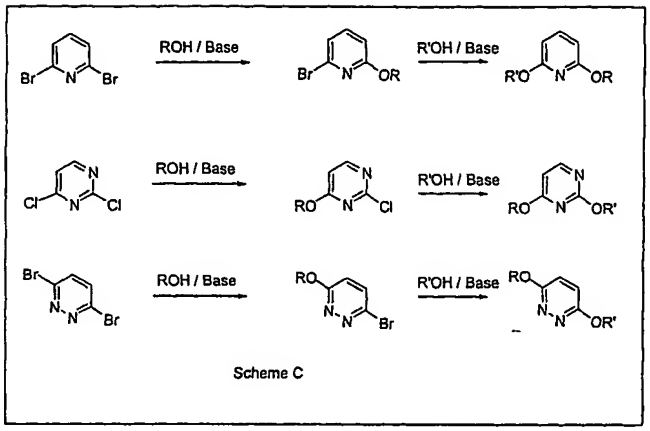


Scheme A-I (For substitution of ArIII)

Bromo substituted heterocycles such as (11 and 12 scheme B) can be converted into the analogous hydroxyl substituted system by first, conversion to the borate ester (13) then oxidative cleavage of the carbon boron bond with an oxidant such as aqueous hydrogen peroxide in the presence of acid or base (such as acetic acid, sodium carbonate or sodium hydroxide) or oxone in the presence of a base (such as sodium carbonate) at or above 0 °C (For

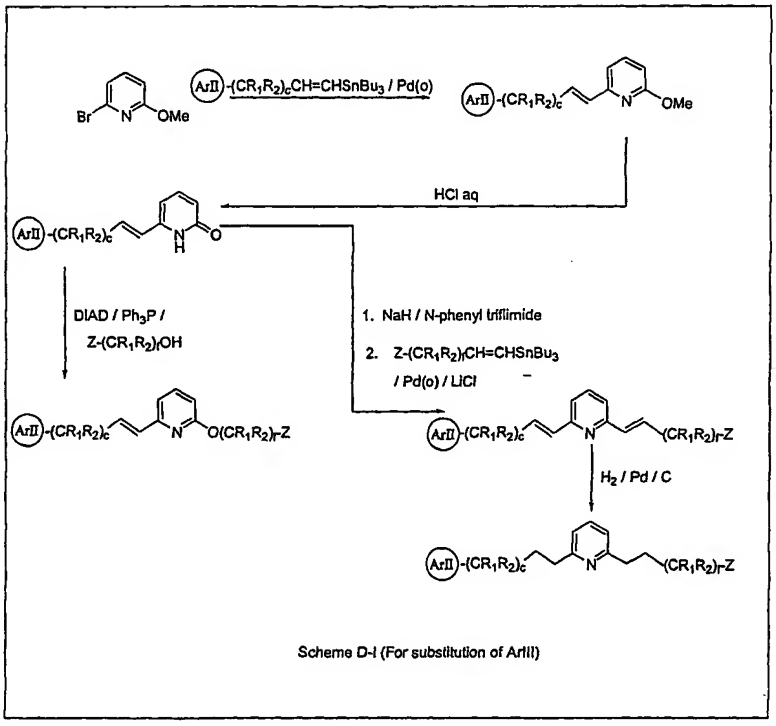


Scheme B (For substitution of Ar II)



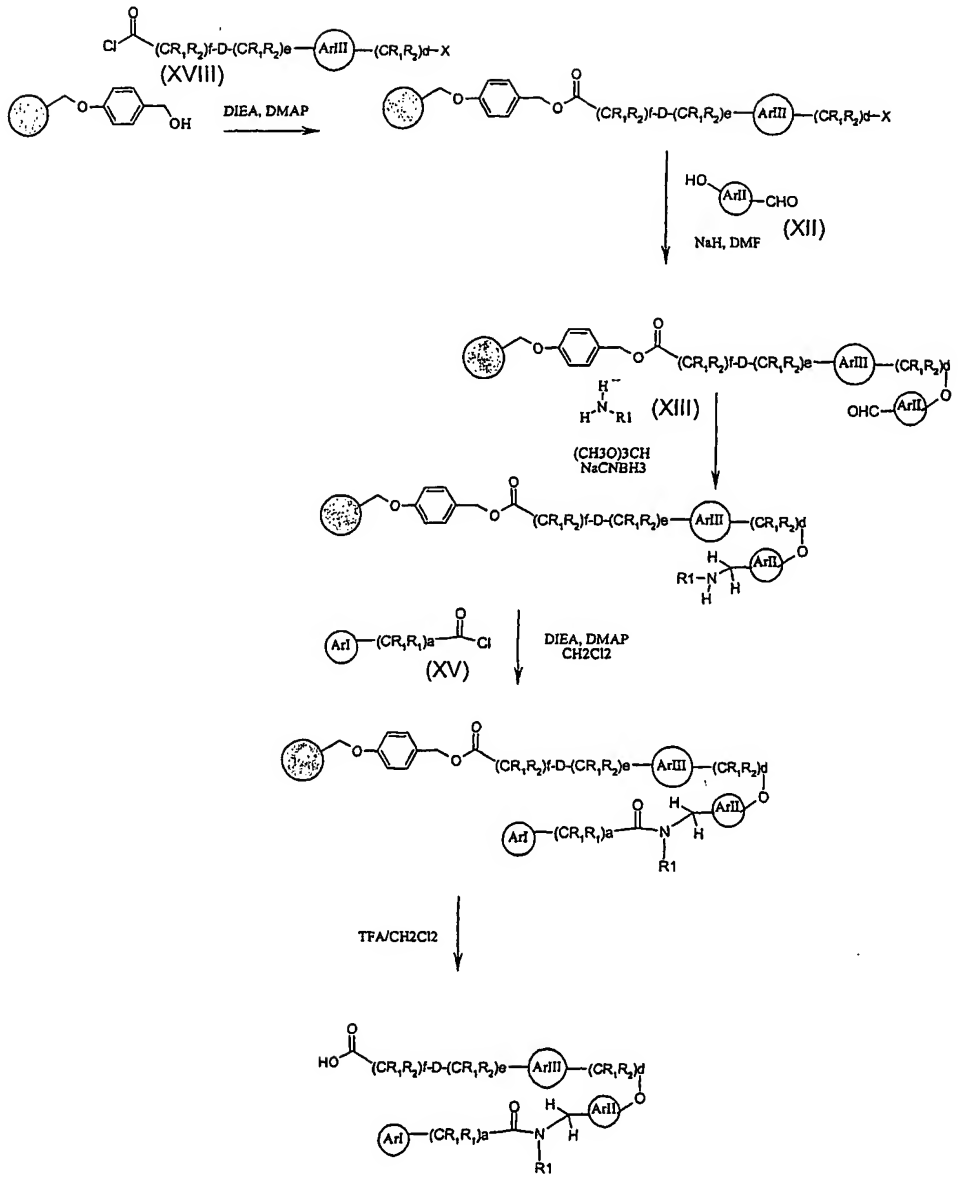
Scheme C

Similar procedures using 2,4-dichloro-pyrimidine or 2,6-dibromo-pyridazine provides the corresponding dialkoxy-substituted pyrimidines and pyridazines. A simple alkoxy group positioned ortho to a nitrogen in these heterocyclic systems can be hydrolysed to the corresponding hydroxy substituent using aqueous hydrochloric acid normally at or above room temperature (Scheme D).



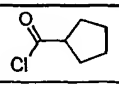
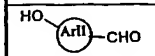
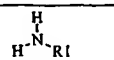
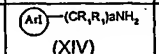
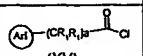
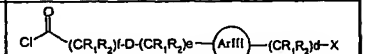
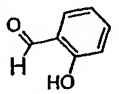
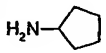
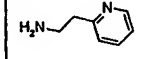
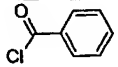
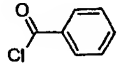
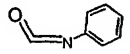
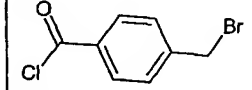
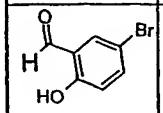
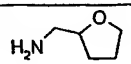
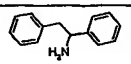
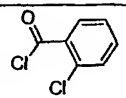
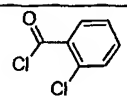
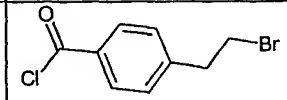
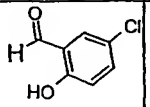
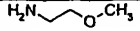
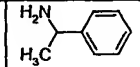
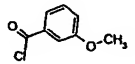
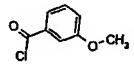
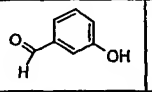
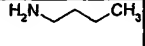
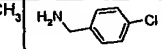
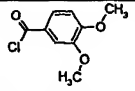
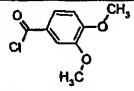
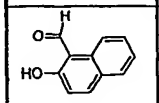
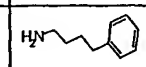
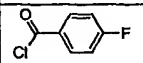
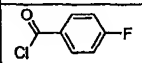
Scheme D-I (For substitution of ArII)

For example, treatment of the 2-methoxy-6-alkenyl-substituted pyridine (17) with hydrochloric acid provides the 6-alkenyl substituted pyridin-2-one. This intermediate, in turn, can be further derivatized to the corresponding 2-alkoxy (18) or 2-alkyl (19) substituted systems as previously described. A methyl, methylene or methine group positioned ortho to a ring nitrogen in these heterocyclic systems can be deprotonated with a base such as an alkyl lithium or LDA in a solvent such as THF ether or HMPA, generally at low temperature (below 0°C) and the resulting anion reacted with electrophiles such as aldehydes epoxides alkyl halides or a,b-unsaturated carbonyl compounds to provide a variety of functionalized side chain substituents.



Scheme F

Table 3

						
 (XII)	 (XIII)	 (XIV)	 (XV)	R_6COCl (XVI)	R_6NCO (XVII)	 (XVIII)
						
						
						
						
						

Compounds useful according to the invention may also be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, for example those described by R. C. Larock in Comprehensive Organic Transformations, VCH publishers, 1989.

In the reactions described hereinafter, it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Green and P.G.M.Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991; J. F. W. McOmie in "Protective Groups in Organic Chemistry" Plenum Press, 1973.

According to a further feature of the present invention, compounds useful according to the invention may be prepared by interconversion of other compounds of the invention.

A compound of the invention including a group containing one or more nitrogen ring atoms, preferably imine (=N-), may be converted to the corresponding compound wherein one or more nitrogen ring atom of the group is oxidized to an N-oxide, preferably by reacting with a peracid, for example peracetic acid in acetic acid or m-chloroperoxybenzoic acid in an inert solvent such as dichloromethane, at a temperature from about room temperature to reflux, preferably at elevated temperature.

The products of this invention may be obtained as racemic mixtures of their dextro and levorotatory isomers since at least one asymmetric carbon atom may be present. When two asymmetric carbon atoms are present, the product may exist as a mixtures of diastereomers based on syn and anti configurations. These diastereomers may be separated by fractional crystallization. Each diastereomer may then be resolved into dextro and levorotatory optical isomers by conventional methods.

It will also be apparent to those skilled in the art that certain compounds of Formula I may exhibit geometrical isomerism. Geometrical isomers include the cis and trans forms of

pharmaceutically acceptable salt by ion exchange procedures. Pharmaceutically acceptable salts useful within the scope of the invention are those derived from the following acids: mineral acids such as hydrochloric acid, trifluoroacetic acid, sulfuric acid, phosphoric acid and sulfamic acid; and organic acids such as acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesufonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, quinic acid, and the like. The corresponding acid addition salts comprise the following: hydrohalides, e.g. hydrochloride and hydrobromide, trifluoroacetate, sulfate, phosphate, nitrate, sulfamate, acetate, citrate, lactate, tartarate, malonate, oxalate, salicylate, propionate, succinate, fumarate, maleate, methylene-bis-β-hydroxynaphthoates, gentisates, mesylates, isothionates, di-p-toluoyltartrates, methanesulfonates, ethanesulfonates, benzenesulfonates, p-toluenesulfonates, cyclohexylsulfamate and quinate, respectively.

The acid addition salts of the compounds useful according to the invention are prepared by reaction of the free base with the appropriate acid, by the application or adaptation of known methods. For example, the acid addition salts of the compounds of this invention are prepared either by dissolving the free base in aqueous or aqueous-alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

The compounds useful according to the invention may be regenerated from the acid addition salts by the application or adaptation of known methods. For example, parent compounds useful according to the invention can be regenerated from their acid addition salts by treatment with an alkali, e.g., aqueous sodium bicarbonate solution or aqueous ammonia solution.

Where the compound useful according to the invention is substituted with an acidic moiety, base addition salts may be formed and are simply a more convenient form for use; in practice, use of the salt form inherently amounts to use of the free acid form. The bases which can be used to prepare the base addition salts include preferably those which produce, when combined with the free acid, pharmaceutically acceptable salts, that is, salts whose cations are

Salt forms useful according to the invention also include compounds having a quarternarized nitrogen. The quarternarized salts are formed by methods such as by alkylation of sp^3 or sp^2 hybridized nitrogen in the compounds.

As will be self-evident to those skilled in the art, some of the compounds useful according to the invention do not form stable salts. However, acid addition salts are most likely to be formed by compounds useful according to the invention having a nitrogen-containing heteroaryl group and/or wherein the compounds contain an amino group as a substituent. Preferable acid addition salts of the compounds useful according to the invention are those wherein there is not an acid labile group.

As well as being useful in themselves as active compounds, the salts of the compounds useful according to the invention are useful for the purposes of purification of the compounds, for example by exploitation of the solubility differences between the salts and the parent compounds, side products and/or starting materials by techniques well known to those skilled in the art.

Various substituents on the compounds useful according to the invention, e.g., as defined in R, R_1 and R_2 can be present in the starting compounds, added to any one of the intermediates or added after formation of the final products by known methods of substitution or conversion reactions. If the substituents themselves are reactive, then the substituents can themselves be protected according to the techniques known in the art. A variety of protecting groups known in the art may be employed. Examples of many of these possible groups may be found in "Protective Groups in Organic Synthesis" by T. W. Green, John Wiley and Sons, 1981. For example, nitro groups can be added to the aromatic ring by nitration, and the nitro group then converted to other groups, such as amino, by reduction, and halo, by diazotization of the amino group and replacement of the diazo group. Acyl groups can be substituted onto the aryl groups by Friedel-Crafts acylation. The acyl groups then can be transformed to the corresponding alkyl groups by various methods, including the Wolff-Kishner reduction and Clemmenson reduction. Amino groups can be alkylated to form mono and dialkylamino groups; and mercapto and hydroxy groups can be alkylated to form corresponding ethers. Primary

4-chloromethylquinoline

2-(β-chloroethyl)quinoline

2-(β-chloropropyl)quinoline

2-(β-chloro-β-phenethyl)quinoline

2-chloromethyl-4-methylquinoline

2-chloromethyl-6-methylquinoline

2-chloromethyl-8-methylquinoline

2-chloromethyl-6-methoxyquinoline

2-chloromethyl-6-nitroquinoline

2-chloromethyl-6,8-dimethylquinoline

EXAMPLE 3

When 3-hydroxybenzyl alcohol of Example 1 above is replaced by the compounds of Table II below then the corresponding product is obtained.

TABLE II

1,2-benzenediol

1,3-benzenediol

1,4-benzenediol

2-mercaptophenol

3-mercaptophenol

4-mercaptophenol

1,3-dimercaptobenzene

1,4-dimercaptobenzene

3-hydroxybenzyl alcohol

3-hydroxyethylphenol

4-hydroxybenzyl alcohol

4-hydroxyethylphenol

2-methylresorsinol

5-methylresorsinol

5-methoxyresorsinol

EXAMPLE 7

3-[3-(2-QUINOLINYLMETHYLOXY)BENZYLOXY]BENZONITRILE

A solution of 0.65 g (5.4 mmol) 3-hydroxybenzonitrile, 1.5 g (5.3 mmol) of 3-(2-quinolinylmethyloxy)benzyl chloride, and 0.75 g (5.4 mmol) of potassium carbonate in 15 ml of DMF is heated at 60°C overnight. The reaction mixture is poured into water. The precipitated product is collected on a filter and purified by dry column chromatography to give 3[3-(2-quinolinylmethyloxy)benzyloxy]benzonitrile. (MP 86-87°C)

EXAMPLE 8

When 3-hydroxybenzonitrile of Example 7 above is replaced by the compounds of Table III below then the corresponding product is obtained.

TABLE III

2-hydroxybenzonitrile
4-hydroxybenzonitrile
2-cyanomethylphenol
3-cyanomethylphenol
4-cyanomethylphenol
2-cyanoethylphenol
3-cyanoethylphenol
4-cyanoethylphenol
2-cyanopropylphenol
3-cyanopropylphenol
4-cyanopropylphenol
3-cyanobutylphenol
4-cyanobutylphenol
2-methyl-3-hydroxybenzonitrile
4-methyl-3-hydroxybenzonitrile
5-methyl-3-hydroxybenzonitrile
2-methyl-4-hydroxybenzonitrile

EXAMPLE 9

When the compounds of Example 6 are used in place of 3-(2-quinolinylmethyloxy)benzyl chloride in Examples 7 and 8 then the corresponding nitriles are obtained.

EXAMPLE 10

5-[3-(3-(2-QUINOLINYLMETHYLOXY)BENZYLOXY)PHENYL]TETRAZOLE

A mixture of 1.2 g (3.28 mmol) of 3-[3-(2-quinolinylmethyloxy)benzyloxy]benzonitrile, 1.89 g (16.4 mmol) of pyridine hydrochloride, and 1.06 g (16.4 mmol) of sodium azide in 10 ml of DMF is heated at 100°C for 4 days. The reaction mixture is poured into water. The crude product collected on a filter and recrystallized from ethyl acetate to give 5-[3-(3-(2-quinolinylmethyloxy)benzyloxy)phenyl]tetrazole. (M.P. 169-172°C.)

EXAMPLE 11

When 4-hydroxybenzyl alcohol is used in place of 3-hydroxybenzyl alcohol in Example 1 and 4-hydroxybenzonitrile is used in place of 3-hydroxybenzonitrile in Example 7 then the product obtained is 5-[4-(4-(2-quinolinylmethyloxy)benzyloxy)phenyl]tetrazole. (M.P. 210-213°C.)

EXAMPLE 12

When 4-cyanomethylphenol is used in place of 4-hydroxybenzonitrile in Example 11 then the product obtained is 5-[4(4-(2-quinolinylmethyloxy)benzyloxy)benzyl]tetrazole. (M.P. 179-181°C.)

EXAMPLE 13

When the nitrile compounds of Example 9 are used in place of 3-[3-(2-quinolinylmethyloxy)benzyloxy]benzonitrile in Example 10 the corresponding tetrazole product is obtained. Representative examples of compounds obtained by this invention are shown in Table IV below.

5-[4-(4-(2-quinolinylmethyloxy)-N-acetyl-benzylamino)phenyl]tetrazole

EXAMPLE 14

METHYL 3-METHOXY-4-[3-(2-QUINOLINYLMETHYLOXY)BENZYLOXY]-BENZOATE

A mixture of 3 g of 3-(2-quinolinylmethyloxy) benzyl chloride, 1.93 g of methyl 4-hydroxy-3-methoxy benzoate, and 1.5 g of potassium carbonate in 30 ml of DMF is heated at 50°C overnight. The reaction mixture is poured into water, the solid product collected on a filter and purified by dry column chromatography to give methyl 3-methoxy-4-(3-(2-quinolinylmethyloxy)benzyloxy)-benzoate. (M.P. 100-101°C.)

EXAMPLE 15

3-METHOXY-4-[3-(2-QUINOLINYLMETHYLOXY)BENZYLOXY]-BENZOIC ACID

A mixture of 2.6 g of methyl 3-methoxy-4-[3-(2-quinolinyl-methyloxy)benzyloxy]benzoate and 0.6 g of NaOH in 15 ml of THF and 2 ml of H_20 are heated at 60°C overnight. The reaction mixture is diluted with 20 ml of H_2O and acidified to pH 4. The product is collected on a filter and dried to give 3-methoxy-4-(3-(2-quinolinylmethyloxy)benzyloxy)benzoic acid. (M.P. 188-190°C.)

EXAMPLE 16

When methyl 4-hydroxy-3-methoxybenzoate is replaced in the procedure of Example 14 with the compounds of Table V, below, then the corresponding products are obtained. Representative examples of compounds prepared by this invention are shown in Table VI.

TABLE V

methyl 2-hydroxybenzoate
methyl 3-hydroxybenzoate
methyl 4-hydroxybenzoate
methyl 3-hydroxy-4-methoxybenzoate
methyl 4-hydroxy-2-methoxybenzoate

TABLE VI

4-(3-(2-quinolinylmethyloxy)benzyloxy)benzoic acid

4-(4-(2-quinolinylmethyloxy)benzyloxy)benzoic acid

3-(4-(2-quinolinylmethyloxy)benzyloxy)benzoic acid

3-(3-(2-quinolinylmethyloxy)benzyloxy)benzoic acid

2-(4-(2-quinolinylmethyloxy)benzyloxy)benzoic acid

4-(3-(2-quinolinylmethyloxy)benzyloxy)phenylacetic acid

4-(3-(2-quinolinylmethyloxy)phenoxy)benzoic acid

4-(3-(2-quinolinylmethyloxy)benzyloxymethyl)benzoic acid

3-methyl-4-(3-(2-quinolinylmethyloxy)benzyloxy)benzoic acid

4-methyl-3-(3-(2-quinolinylmethyloxy)benzyloxy)benzoic acid

2-methyl-4-(3-(2-quinolinylmethyloxy)benzyloxy)benzoic acid

3-methoxy-4-(3-(2-quinolinylmethyloxy)benzyloxy)benzoic acid

4-methoxy-3-(3-(2-quinolinylmethyloxy)benzyloxy)benzoic acid

2,6-dimethyl-4-(3-(2-quinolinylmethyloxy)benzyloxybenzoic acid

4-(3-(2-quinolinylmethyloxy)benzylthio)benzoic acid

4-(3-(2-quinolinylmethyloxy)benzylamino)benzoic acid

EXAMPLE 17

3-METHOXY-4-(3-(2-QUINOLINYLMETHYLOXY) PHENOXYMETHYL)BENZOYL-N-BENZENESULFONAMIDE

A reaction mixture of 0.73 g of 3-methoxy-4-(3-(2-quinolinyl-methyloxy)phenoxy)benzoic acid, 0.28 g of benzenesulfonamide, 0.28 g of 4-dimethylpyridine, and 0.44 g of 1-(3-dimethylamino-propyl)-3-ethylcarbodimide hydrochloride in 50 ml of CH_2Cl_2 is stirred at room temperature overnight. The solvent is removed and the residue is extracted into ethyl acetate. The organic solution is washed with water, and evaporated. The product is purified by dry column chromatography to give 3-methoxy-4-(3-(2quinolinylmethyloxy) phenoxymethyl)benzoyl-N-benzenesulfonamide. (M.P. 156-158°C.)

EXAMPLE 22

When the procedures of Examples 19 and 20 are followed and methyl 3-chloromethylbenzoate is replaced by methyl 3-methoxy-4-chloromethylbenzoate then the product prepared is 3-methoxy-4-(3-(2-quinolinylmethyloxy)phenoxymethyl)benzoic acid. (M.P. 208-210°C.)

EXAMPLE 23

When the procedure of Example 19 is followed and the compounds of Table VII below are used in place of methyl-3-chloromethyl-benzoate then the corresponding product is obtained.

TABLE VII

ethyl 2-chloromethylbenzoate
ethyl 3-chloromethylbenzoate
ethyl 4-chloromethylbenzoate
ethyl 3-chloromethylbenzoate
methyl 4-chloromethylbenzoate
methyl 2-methyl-5-chloromethylbenzoate
methyl 2-methyl-3-chloromethylbenzoate
methyl 3-methyl-5-chloromethylbenzoate
methyl 4-methyl-5-chloromethylbenzoate
methyl 2-methyl-4-chloromethylbenzoate
methyl 3-methyl-4-chloromethylbenzoate
methyl 2-methoxy-5-chloromethylbenzoate
methyl 2-methoxy-3-chloromethylbenzoate
methyl 2-methoxy-4-chloromethylbenzoate
methyl 3-methoxy-4-chloromethylbenzoate
methyl 3-chloromethylphenylacetate
methyl 4-chloromethylphenylacetate
methyl 3-chloromethylphenylpropionate
methyl 4-chloromethylphenylpropionate

N-acetyl-4-(2-quinolinylmethyloxy)phenylamine

EXAMPLE 25

When the procedures of Examples 19 and 20 are followed using the compounds of Table VII, Example 23 and Table VIII, Example 24, then the corresponding product is obtained. Representative examples of compounds prepared by this invention are shown in Table IX.

TABLE IX

3-(4-(2-quinolinylmethyloxy)phenoxymethyl)benzoic acid

4-(4-(2-quinolinylmethyloxy)phenoxymethyl)benzoic acid

2-(3-(2-quinolinylmethyloxy)phenoxymethyl)benzoic acid

2-(4-(2-quinolinylmethyloxy)phenoxymethyl)benzoic acid

2-methyl-3-(3-(2-quinolinylmethyloxy)phenoxymethyl)benzoic acid

2-ethyl-3-(3-(2-quinolinylmethyloxy)phenoxymethyl)benzoic acid

2-methoxy-3-(3-(2-quinolinylmethyloxy)phenoxymethyl)benzoic acid

3-methyl-4-(3-(2-quinolinylmethyloxy)phenoxymethyl)benzoic acid

2-methyl-4-(3-(2-quinolinylmethyloxy)phenoxymethyl)benzoic acid

2-methoxy-4-(3-(2-quinolinylmethyloxy)phenoxymethyl)benzoic acid

3-(3-(2-quinolinylmethyloxy)-5-methylphenoxymethyl)benzoic acid

3-(3-(2-quinolinylmethyloxy)-5-methoxyphenoxymethyl)benzoic .acid

3-(4-(2-quinolinylmethyloxy)-3-methylphenoxymethyl)benzoic acid

3-(4-(2-quinolinylmethyloxy)-2-methylphenoxymethyl)benzoic acid

2-methyl-3-(3-(2-quinolinylmethyloxy)-2-methylphenoxymethyl)benzoic acid

3-(3-(2-quinolinylmethylthio)phenoxymethyl)benzoic acid

4-(4-(2-quinolinylmethylthio)phenoxymethyl)benzoic acid

3-(3-(2-quinolinylmethyloxy)phenoxymethyl)phenylacetic acid

3-(3-(2-quinolinylmethyloxy)phenoxymethyl)phenylpropionic acid

3-(3-(2-quinolinylmethyloxy)phenylthiomethyl)benzoic acid

4-(3-(2-quinolinylmethyloxy)phenylthiomethyl)benzoic acid

3-(4-(2-quinolinylmethyloxy)phenylthiomethyl)benzoic acid

m(cyanomethyl)benzyl bromide, and p-(cyanomethyl)- benzyl bromide, then the products prepared are:

5-(2-(3-(2-quinolinylmethyloxy)phenoxymethyl)phenyl)tetrazole (M.P. 166-170°C);
5-(3-(3-(2-quinolinylmethyloxy)phenoxymethyl)phenyl)tetrazole (M.P. 115°C dec.);
5-(2-(3-(2-quinolinylmethyloxy)phenoxymethyl)benzyl)tetrazole (M.P. 145.5-147°C);
5-3-(3-(2-quinolinylmethyloxy)phenoxymethyl)benzyl)tetrazole (M.P. 161-164°C); and
5-(4-(3-(2-quinolinylmethyloxy)phenoxymethyl)benzyl)tetrazole (M.P. 149-152°C).

EXAMPLE 29

When the procedure of Example 26 is followed and the compounds of Table X below are used in place of p-cyanobenzyl bromide then the corresponding product is obtained.

TABLE X

2-methyl-4-cyanobenzyl bromide
3-methyl-4-cyanobenzyl bromide
3-methoxy-2-cyanobenzyl bromide
2-methyl-3-cyanobenzyl bromide
3-cyano-4-methylbenzyl bromide
4-methoxy-2-cyanobenzyl bromide
3-cyano-5-methylbenzyl bromide
2-methyl-5-cyanobenzyl bromide
2-methoxy-5-cyanobenzyl bromide
2-methoxy-4-cyanobenzyl bromide
2-methoxy-3-cyanobenzyl bromide
2,6-dimethyl-4-cyanobenzyl bromide
3-methoxy-4-cyanobenzyl bromide
2-methyl-6-cyanobenzyl bromide
o-cyanobenzyl bromide
m-cyanobenzyl bromide
p-cyanobenzyl bromide

EXAMPLE 31

When the procedures of Examples 26 and 27 are followed using the compounds of Table X, Example 29 and the appropriate alcohol, thio or amino salt formed in Example 30, then the corresponding products are obtained. Representative examples of compounds prepared by this invention are shown in Table XI.

TABLE XI

5-(4-(4-(2-quinolinylmethyloxy)phenoxymethyl)phenyl)tetrazole

5-(3-(4-(2-quinolinylmethyloxy)phenoxymethyl)phenyl)tetrazole

5-(3-(2-(2-quinolinylmethyloxy)phenoxymethyl)phenyl)tetrazole

5-(2-(4-(2-quinolinylmethyloxy)phenoxymethyl)phenyl)tetrazole

5-(4-(2-(2-quinolinylmethyloxy)phenoxymethyl)phenyl)tetrazole

5-(2-(2-(2-quinolinylmethyloxy)phenoxymethyl)phenyl)tetrazole

5-(3-(3-(2-quinolinylmethyloxy)phenoxymethyl)phenyl)tetrazole

5-(4-(3-(2-quinolinylmethyloxy)-5-methoxyphenoxymethyl)phenyl)tetrazole

5-(4-(3-(2-quinolinylmethyloxy)-5-methylphenoxymethyl)phenyl)tetrazole

5-(3-(4-(2-quinolinylmethyloxy)-2-methylphenoxymethyl)phenyl)tetrazole

5-(3-(4-(2-quinolinylmethyloxy)-2-methoxyphenoxymethyl)phenyl)tetrazole

5-(4-(3-(2-quinolinylmethyloxy)-2-methylphenoxymethyl)phenyl)tetrazole

5-(4-(4-(2-quinolinylmethyloxy)-2-methylphenoxymethyl)phenyl)tetrazole

5-(4-(4-(2-quinolinylmethyloxy)-3-methylphenoxymethyl)phenyl)tetrazole

5-(4-(3-(2-quinolinylmethylthio)phenoxymethyl)phenyl)tetrazole

5-(3-(3-(2-quinolinylmethylthio)phenoxymethyl)phenyl)tetrazole

5-(2-(3-(2-quinolinylmethylthio)phenoxymethyl)phenyl)tetrazole

5-(2-(4-(2-quinolinylmethyloxy)phenoxymethyl)benzyl)tetrazole

5-(4-(4-(2-quinolinylmethyloxy)phenoxymethyl)benzyl)tetrazole

5-(3-(4-(2-quinolinylmethyloxy)phenoxymethyl)benzyl)tetrazole

5-(4-(3-(2-quinolinylmethyloxy)phenoxymethyl)phenethyl)tetrazole

5-(3-(2-(4-(2-quinolinylmethyloxy)phenoxymethyl)phenyl)propyl)tetrazole

5-(4-(3-(2-(2-quinolinylmethyloxy)phenoxymethyl)phenyl)butyl)tetrazole

5-(2-(4-(3-(2-quinolinylmethyloxy)phenoxymethyl)phenyl)propyl)tetrazole

solution is washed with water and brine, then evaporated to give α-(3-chloromethylphenoxy)acetonitrile as a yellow oil which is used directly in the next step.

C. α-(3-(4-(2-quinolinylmethyloxy)phenoxymethyl)phenoxy)acetonitrile

A mixture of α-(3-chloromethylphenoxy)acetonitrile (0.025 mol), sodium 4-(2-quinolinylmethyloxy)phenoxide (0.025 mol) and anhydrous potassium carbonate (0.125 mol) in dimethylsulfoxide (50 ml) is stirred at ambient temperature for 18 hrs. The reaction is diluted with water (600 ml) and extracted with ethyl acetate (3x150 ml). The ethyl acetate solution is washed with water (3x100 ml) and brine (100 ml) then dried and evaporated to give α-(3-(4-(2-quinolinylmethyloxy)phenoxymethyl)phenoxy)acetonitrile. (M.P. 110-114°C.)

D. 5-(3-(4-(2-quinolinylmethyloxy)phenoxymethyl)phenoxymethyl)tetrazole

α-(3-(4-(2-quinolinylmethyloxy)phenoxymethyl)phenoxy)acetonitrile (8.12 mmol), sodium azide (24.4 mmol) and ammonium chloride (24.4 mmol) in dimethylformamide (10 ml) are heated at 115-120°C for 6 hrs. After cooling, the reaction mixture is diluted with ethyl acetate (150 ml), washed with water (6x100 ml) then dried and evaporated. The residue is chromatographed on a column of silica gel (360 g) and eluted with a gradient of isopropanol in methylene chloride to give 5-(3-(4-(2-quinolinylmethyl-oxy)phenoxymethyl)phenoxymethyl)tetrazole. (M.P. 131-32°C.)

EXAMPLE 33

When sodium 4-(2-quinolinylmethyloxy)phenoxide of Example 32, Step C, is replaced with sodium 3-(2-quinolinylmethyloxy)phenoxide, the product prepared is 5-(3-(3-(2-quinolinylmethyloxy)phenoxymethyl)phenoxymethyl)tetrazole. (M.P. 135-137°C.)

EXAMPLE 34

When α-(3-hydroxymethylphenoxy)acetonitrile of Example 32, Step B. is replaced with α-(4-hydroxymethylphenoxy)acetonitrile then the product prepared is 5-(4-(3-(2 quinolinylmethyloxy)phenoxymethyl)phenoxymethyl)tetrazole. (M.P. 154-156°C.)

3-hydroxymethyl-N-acetylamidine
4-hydroxymethyl-N-acetylamidine
4-hydroxymethylamidine
4-methyl-2-hydroxymethylphenol
2-methyl-5-hydroxymethylphenol
4-methyl-3-hydroxymethylphenol
5-methyl-3-hydroxymethylphenol
3-methyl-4-hydroxymethylphenol
2-methyl-4-hydroxymethylphenol
3-methyl-5-hydroxymethylphenol
4-methoxy-3-hydroxymethylphenol
3-methoxy-4-hydroxymethylphenol
2-methoxy-4-hydroxymethylphenol
5-methoxy-3-hydroxymethylphenol
3-methoxy-5-hydroxymethylphenol
2-methoxy-5-hydroxymethylphenol
2-(1'-hydroxyethyl)phenol
3-(1'-hydroxyethyl)phenol
4-(1'-hydroxyethyl)phenol
2-(2'-hydroxyethyl)phenol
3-(2'-hydroxyethyl)phenol
4-(2'-hydroxyethyl)phenol
2-(3'-hydroxypropyl)phenol
3-(3'-hydroxypropyl)phenol
4-(3'-hydroxypropyl)phenol
2-(2'-hydroxypropyl)phenol
3-(2'-hydroxypropyl)phenol
4-(2'-hydroxypropyl)phenol
2-(1'-hydroxypropyl)phenol
3-(1'-hydroxypropyl)phenol
4-(1'-hydroxypropyl)phenol

5-(4-(4-(2-quinolinylmethyloxy)-2-methylphenoxymethyl)-3-methylphenoxymethyl)tetrazole

5-(4-(4-(2-quinolinylmethyloxy)-3-methylphenoxymethyl)-2-methylphenoxymethyl)tetrazole

5-(2-(3-(4-(2-quinolinylmethyloxy)phenoxymethyl)phenoxy)ethyl)tetrazole

5-(3-(3-(4-(2-quinolinylmethyloxy)phenoxymethyl)phenoxy)propyl)tetrazole

5-(2-(3-(4-(2-quinolinylmethyloxy)phenoxymethyl)phenoxy)propyl)tetrazole

5-(3-(3-(4-(2-quinolinylmethyloxy)phenoxymethyl)phenoxy)butyl)tetrazole

5-(4-(4-(2-quinolinylmethyloxy)phenylthiomethyl)phenoxymethyl)tetrazole

5-(4-(4-(2-quinolinylmethyloxy)phenylthiomethyl)phenylthiomethyl)tetrazole

5-(4-(4-(2-quinolinylmethylthio)phenoxymethyl)phenoxymethyl)tetrazole

5-(4-(4-(2-quinolinylmethyloxy)phenoxymethyl)phenyl-N-acetylaminomethyl)tetrazole

5-(3-(4-(4-(2-quinolinylmethyloxy)phenoxymethyl)phenylthio)butyl)tetrazole

5-(3-(3-(4-(2-quinolinylmethyloxy)phenoxy-1'-ethyl)phenoxymethyl)tetrazole

5-(3-(3-(4-(2-quinolinylmethyloxy)phenoxy-2'-propyl)phenoxymethyl)tetrazole

5-(3-(3-(4-(2-quinolinylmethyloxy)phenoxy-3'-butyl)phenoxymethyl)tetrazole

EXAMPLE 39

3-(3-(2-QUINOLINYLMETHYLOXY)BENZYLOXY)BENZALDEHYDE

When 3-hydroxybenzonitrile in Example 7 is replaced by 3-hydroxybenzaldehyde then the product prepared is 3-[3-(2-quinolinylmethyloxy)benzyloxy)benzaldehyde.

EXAMPLE 40

When 3-hydroxybenzaldehyde of Example 39 is replaced by the compounds of Table XIV below, then the corresponding product is obtained.

TABLE XIV

2-hydroxybenzaldehyde

4-hydroxybenzaldehyde

2-methyl-3-hydroxybenzaldehyde

5-methyl-3-hydroxybenzaldehyde

2-methyl-4-hydroxybenzaldehyde

EXAMPLE 43

When 3-(3-(2-quinolinylmethyloxy)benzyloxy)benzaldehyde of Example 42 is replaced by the compounds of Example 41, the corresponding product is prepared.

When diethylcyanomethylphosphonate in the above Example is replaced by diethylcyanoethylphosphate, diethylcyanopropylphospate or diethylcyanoisopropylphosphate then the corresponding products are obtained.

EXAMPLE 44

5-(3-(3-(2-QUINOLINYLMETHYLOXY)BENZYLOXY)STYRYLTETRAZOLE HYDROCHLORIDE

A mixture of 3-(3-(2-quinolinylmethyloxy)benzyloxy)cinnamylnitrile (0.03 mol), anhydrous aluminum chloride (0.03 mol) and sodium azide (0.09 mol) in THF (30 ml) is stirred and refluxed for 18 hours. Hydrochloric acid (18% HCl 15 ml) is added and thereafter the reaction mixture is poured into ice water. The precipitate is collected and then recrystalized from methanol-ethyl acetate to obtain pure 5-(3-(3-(2-quinolinylmethyloxy)benzyloxy)styryl)tetrazole hydrochloride.

The free base is obtained by treatment of the salt with one equivalent of sodium hydroxide solution followed by removal of sodium chloride and water.

EXAMPLE 45

When 3-(3-(2-quinolinylmethyloxy)benzyloxy)cinnamylnitrile of Example 44 is replaced by the compounds formed in Example 43, then the corresponding product is prepared. Representative compounds prepared by this invention are described in Table XV.

TABLE XV

5-(4-(3-(2-quinolinylmethyloxy)phenoxy)styryl)tetrazole

5-(4-(3-(2-quinolinylmethyloxy)benzyloxy)styryl)tetrazole

5-(3-(4-(2-quinolinylmethyloxy)benzyloxy)styryl)tetrazole

washed with water, and then ethyl acetate to give
5-(4-(3-(2-quinolinylmethyloxy)phenoxymethyl)phenyl)tetrazol-3-yl acetic acid.

In a similar manner, the substituted tetrazoles of this invention may be prepared.

EXAMPLE 48

4-(4-(2-QUINOLINYLMETHYLSULFONYL)PHENOXYMETHYL)BENZOIC ACID

A. 4-(4-(2-quinolinylmethylthio)phenoxymethyl)benzoic acid (4 mmol) in dichloroethene (50 ml) is stirred with m-chloroperbenzoic acid (4 mmol) and solid potassium hydrogen carbonate (1.0 g). The reaction is assayed by TLC and upon consumption of the starting thio compound, the mixture is filtered, washed with dilute aqueous sodium bisulfite, dried and evaporated to give 4-(4-(2-quinolinylmethylsulfinyl)phenoxymethyl)benzoic acid.

B. To 3 mmol of the sulfinyl compound from Step A in acetic acid (40 mmol) is added 30% hydrogen peroxide (2 ml). The mixture is stirred at ambient temperature and assayed by TLC. Upon disappearance of the sulfinyl starting compound, the reaction mixture is diluted with dichloromethane, washed with dilute aqueous sodium bisulfite and water, dried and evaporated to give 4-(4-(2-quinolinylmethylsulfonyl)phenoxymethyl)benzoic acid.

In a similar manner, the sulfinyl and sulfonyl compounds of this invention may be prepared.

EXAMPLE 49

5-(3-METHYL-4-(4-(4-(2-QUINOLINYLMETHYLOXY)BENZYLOXY)-PHENYL)BUTYL)TETRAZOLE

A. 4-benzyloxy-α-methyl-cinnamic acid ethyl ester.

To a solution of sodium hydride (60% oil dispersion, 3.1 g) and diethyl 2-phosphonopropionate (15.5 g) in tetrahydrofuran (50 ml) is added dropwise a tetrahydrofuran

F. 4-methyl-5-(4-(4-(2-quinolinyloxymethyl)benzyloxy)phenyl)valeronitrile.

A reaction mixture of 5-hydroxyphenyl-4-methyl-valeronitrile (2.9 g), 4-(2-quinolinylmethyloxy)benzyl chloride hydrochloride (6.3 g) and anhydrous potassium carbonate (30 g) in dimethylformamide (60 ml) is stirred and heated (110°C) for 5 hours. Afterward, the solvent is removed under vacuum and the residue is partitioned in a mixture of chloroform/water. The organic layer is evaporated and the resultant oil is purified on a silica gel dry column (chloroform as eluant) to give product which may used directly in the next step.

G. 5-(3-methyl-4-(4-(4-(2-quinolinylmethyloxy)- benzyloxy)phenyl)butyl)tetrazole.

A mixture of 4-methyl- 5(4-(4-(2-quinolinylmethyloxy)benzyloxy)phenyl)valeronitrile (1.5 g.), sodium azide (3 g), ammonium chloride (1.9 g) in dimethylformamide (20 ml) is stirred and heated at 135°C for 18 hours. After cooling, the reaction mixture is poured into ice water and the insoluble material is taken up by chloroform. The residue from the evaporation of chloroform is purified by silica gel dry column (5% methanol chloroform as eluant) to yield 5-(3-methyl-4-(4-(4-(2-quinolinylmethyloxy)benzyloxy)-phenyl)butyl)tetrazole.

EXAMPLE 50

When 2-chloromethylquinoline of Example 49, Part F is replaced by the quinoline compounds of Examples 5 and 6, then the corresponding product is obtained. When the products are treated according to the procedures of Steps F and G. then the corresponding tetrazole products are obtained.

EXAMPLE 51

When diethyl 2-phosponopropionate of Example 49, Step A is replaced by the Wittig reagents of Table XVI below then the corresponding products are obtained.

TABLE XVI

diethyl 2-phosphonoacetate

diethyl 2-phosphonopropionate

diethyl 3-phosphonopropionate

diethyl 4-phosphonobutyrate

diethyl 3-phosphonopentanonitrile
diethyl 2-phosphonopentanonitrile
diethyl 4-phosphono-5-phenylpentanonitrile
diethyl 4-phosphono-3-phenylbutyronitrile
diethyl 4-phosphono-5-cyclopropylpentanonitrile
diethyl 4-phosphonohexanonitrile
diethyl 4-phosphonoheptanonitrile
diethyl 4-phosphono-5-carbethoxypentanonitrile
diethyl 4-phosphono-3-methylenebutyronitrile
diethyl 4-phosphono-3-ethylidenebutyronitrile
diethyl l-phosphonomethyl-1-cyanoethylcyclopropane
diethyl l-phosphonomethyl-1-cyanomethylcyclobutane
diethyl l-phosphonomethyl-2-cyanomethylcyclobutane
diethyl l-phosphonomethyl-2-cyanomethylcyclopentane

EXAMPLE 53

When diethyl 2-phosphonopropionate of Example 49, Step A is replaced by the Wittig reagents of Table XVII, Example 52, then the corresponding products are obtained. When these products are treated according to the procedure of Example 50, then the corresponding product is obtained.

EXAMPLE 54

When 4-hydroxy-3-methoxybenzoate of Example 14 is replaced with 3-hydroxymethylphenol, then the product prepared is 3-(3-(2-quinolinylmethyloxy)benzyloxy)benzyl alcohol.

EXAMPLE 55

When 4-hydroxy-3-methoxybenzoate of Example 14 is replaced with the compounds of Table XVIII below and 3-(2-quinolinylmethyloxy)benzyl chloride is replaced by the compounds of Example 6, then the corresponding products are prepared.

TABLE XIX

chloroacetonitrile

bromoacetonitrile

3-chloropropionitrile

4-chlorobutyronitrile

5-chloropentanonitrile

6-chlorohexanonitrile

2-chloropropionitrile

2-methyl-3-chloropropionitrile

2-chlorobutyronitrile

3-chlorobutyronitrile

4-methyl-5-chloropentanonitrile

2-methyl-3-chloropropionitrile

3-benzyl-4-chlorobutyronitrile

3-carbethoxymethyl-4-chlorobutyronitrile

3-methoxymethyl-4-chlorobutyronitrile

2,3-dimethyl-4-chloropentanonitrile

3,3-dimethyl-4-chloropentanonitrile

spiro-(3,3-cyclopropane)-4-chlorobutyronitrile

l-chloromethyl-2-cyanomethylcyclobutane

l-chloromethyl-2-cyanomethylcyclohexane

3-cyclopropylmethyl-4-chlorobutyronitrile

3-dimethylaminomethyl-4-chlorobutyronitrile

3-methylene-4-chlorobutyronitrile

3-propylidene-4-chlorobutyronitrile

EXAMPLE 58

5-(4-(3-(3-(2-QUINOLINYLMETHYLOXY)BENZYLOXY)PHENYL)BUTYL)-TETRAZOLE

A mixture of (0.014 mol) 3-(3-(2-quinolinylmethyloxy)benzyloxy)benzyl alcohol (0.14 mol) 5-(3-chloropropyl)tetrazole and 2 g (O.036 mol) KOH in 5 ml water and 50 ml ethanol is

EXAMPLE 62

5-(4-(3-(2-QUINOLINYLMETHYLOXY)BENZOYLMETHYL)PHENYL)TETRAZOLE

A. 2-(3-(2-quinolinylmethyloxy(phenyl)-l,3-dithiane.

A 1M solution of 3-(2-quinolinylmethyloxy)benzaldehyde (0.01 mol) in chloroform is combined with an equimolar amount of 1,3 propane-dithiol at -20°C. Dry HCl gas is slowly passed through the solution for 5-10 minutes. The reaction mixture is then allowed to come to room temperature. After 3 hours, the reaction mixture is worked up by successively washing with water, 10% aqueous KOH and water and drying over K2CO3. Evaporation of the solvent furnishes the desired product which is purified by column chromatography to give product which is used directly in the next step.

B. 2-(3-(2-quinolinylmethyloxy)phenyl-2-(p-cyanobenzyl)- 1,3-dithiane.

To a 0.2M THF solution of the 2-(3-(2quinolinyl-methyloxy)phenyl)-1,3-dithiane (0.01 mol) under is added a 5% excess of N-butyl lithium in N-hexane (2.5M) at a rate if 3-5 ml/min at -78°C. After 3 hours, 4-cyanobenzylchloride (0.01 mol in 20 ml of THF) is added dropwise over a period of 10 minutes. Let stir 3 hours at -78°C and then allow the reaction mixture to come to 0°C slowly. The mixture is poured into 3 volumes of water, extracted with chloroform furnishing an organic solution which is washed twice with water, 7% aqueous KOH and again with water. The organic layer is dried over K2CO3 and is concentrated. The crude product is purified by column chromatography to give the desired product which is used directly in the next step.

C. 4-(3-(2-quinolinylmethyloxy)benzoylmethyl)benzonitrile.

To a solution of 2-(3-(2-quinolinylmethyloxy)-1,3- dithiane (1.0 mmol) in 80% aqueous acetonitrile (10 ml) is added mercuric chloride (2.2 mmol) as a solution in the same solvent mixture. Mercuric oxide (1.1 mmol) is then added to buffer the reaction mixture near pH=7. The dithiane - mercuric chloride complex separates as a white precipitate. The reaction mixture is refluxed under nitrogen for 5 hours, then cooled and filtered through Super Gel. The filter cake is washed thoroughly with 1:1 hexane-dichloromethane. The organic phase is washed with 5 M aqueous ammonium acetate, water and brine. The organic phase is then dried with $MgSO_4$,

B. 3-(2-quinolinylmethyloxy)benzoic acid chloride.

A mixture of 15.6 g (0.1 mol) of 3-(2-quinolinylmethyloxy)benzoic acid and 11.9 g (0.1 mol) of thionyl chloride is refluxed for 4 hours. The reaction mixture is then evaporated to dryness at room temperature and used directly in the next step.

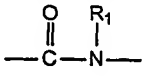
C. 3-(3-(2-quinolinylmethyloxy)benzoylamino)benzonitrile.

A solution of 3-aminobenzonitrile (10 mmol) in 50 ml of chloroform and triethylamine (11 mmol) is added to a solution of 10 mmol of 3-(2-quinolinylmethyloxy)benzoic acid chloride in 20 ml of chloroform over a period of 10 minutes. The reaction is stirred at room temperature for 2 hours and is poured into water and then extracted into chloroform. The organic solution is dried and evaporated to give 3-(3-(2-quinolinylmethyloxy)benzoylamino)benzonitrile.

D. 5-(3-(3-(2-quinolinylmethyloxy)benzoylamino)phenyl)tetrazole.

A mixture of 10 mmol of 3-(3-(2-quinolinylmethyloxy)benzoylamino)benzonitrile, 50 mmol of sodium azide, and 50 mmol of pyridine HCl in 30 ml of DMF is heated at 100°C for 2 days. The reaction mixture is poured into water, and the product is collected on a filter. Recrystallization from ethyl acetate and DMF gives 5-(3-(3-(2-quinolinylmethyloxy)-benzoylamino)phenyl)tetrazole.

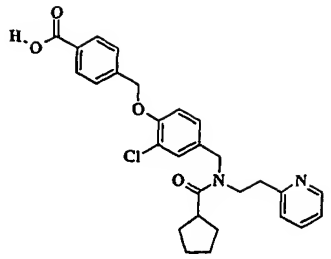
In a similar manner, the compounds of this invention

where B is  may be made.

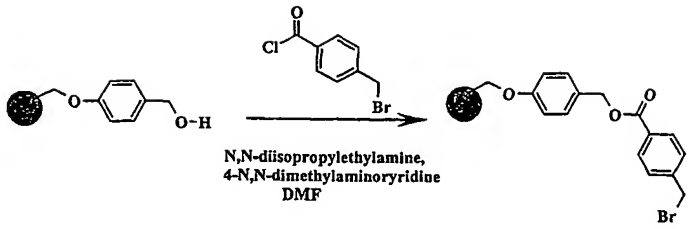
EXAMPLE 65

5-(3-(3-(2-QUINOLINYLMETHYLOXY)-ANILINOCARBONYL)PHENYL)TETRAZOLE

When the procedure of Example 64 is followed and 3-(2-quinolinylmethyloxy)aniline is used in place of 3-aminobenzonitrile and 3-cyanobenzoic acid is used in place of 3-(2-quinolinylmethyloxy) benzoic acid, then the product prepared is 5-(3-(3-(2-quinolinylmethyloxy)anilinocarbonyl)phenyl)tetrazole.



1. Acid Loading:

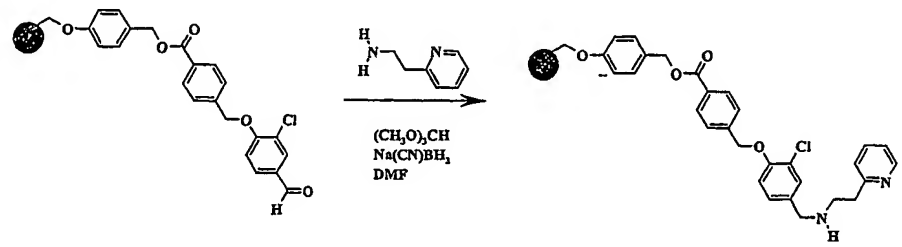


A 1L round bottom flask is charged with 4-(bromomethyl)benzoic acid (32.26 g, 150.0 mmole) and dichloromethane (650 mL). A stir bar is carefully added and the reaction flask is immersed in an ice-water bath. After approximately 15 minutes, oxallyl chloride (15.7 mL, 180 moles) is added. After approximately 15 minutes, N,N-dimethylformaide (500 mL, cat.) is added. The reaction began to bubble. After stirring for 1.5 hours, the ice-water bath is removed. After stirring for 3 hours at ambient temperature, the effervescence has ceased. At the end of this period, the stirbar is removed from the reaction mixture and the reaction solvent is removed in vacuo. After the solvent has been removed, more dichloromethane is added to the reaction flask and this too is removed in vacuo.

A three neck 3L round bottom flask is charged with dry N,N-dimethylformamide (1.3 L), N,N-diisopropylethylamine (39.19 mL, 225 mmoles), 4-N,N-dimethylaminopyridine (3.67 g, 30 mmole) and MicroKANS [1456, 15 mg of Wang resin (1.7 mmole/g loading) per MicroKANs, 25.5 micromoles/microKAN, 37.1 mmoles]. The flask is fitted with an overhead stirring apparatus. After stirring for approximately 15 minutes, a solution of the acid chloride as prepared above in dry N,N-dimethylformamide (200 mL) is transferred into the reaction flask.

methanol (1 x 4 L), dichloromethane (1 x 4 L) then methanol (1 x 4 L), dichloromethane (1 x 4 L) then methanol (1 x 4 L), dichloromethane (1 x 4 L) and ether (1 x 4 L). After the final washing the MicroKANs are dried by blowing a stream of nitrogen through the flask with intermittent agitation. After sufficient drying, the MicroKANs are sorted for the next reaction.

3. Reductive Amination:



A three neck 2 L round bottom flask is charged with the MicroKANs [784, 25.5 micromoles/microKAN, 20.0 mmoles], trimethylorthoformate (850 mL) and 2-(2-aminoethyl)pyridine 20.79 g, 170 mmoles). The reaction flask is fitted with an overhead stirrer. After 2 hours, sodium cyanoborohydride (21.37 g, 340 mmoles) is added. After approximately 10 minutes, acetic acid (17.0 mL, 297 mmoles) is added. After stirring for an additional hour, the reaction flask is drained. Methanol (800 mL) is added to the flask. After stirring for approximately 10 minutes, the flask is drained. the reaction flask is washed repeatedly in the following sequence: DMF (3 x 4 L), dichloromethane (1 x 4 L) then methanol (1 x 4 L), dichloromethane (1 x 4 L) then methanol (1 x 4 L), dichloromethane (1 x 4 L) then methanol (1 x 4 L), dichloromethane (1 x 4 L) and ether (1 x 4 L). After the final washing the microKANS are dried by blowing a stream of nitrogen through the flask with intermittent agitation. After sufficient drying, the MicroKANs are sorted for the next reaction.

4. Acylation:

The methods described above are used to prepare the following compounds of this invention.

5-[2-(4-(2-quinolinylmethoxy)phenoxymethyl)benzyl]tetrazole (M.P. 108-111°C)
CALC: C, 59.87; H, 5.96; N, 13.96
FOUND: C, 59.67, 60.01; H, 5.62, 5.63; N,. 13,73, 13.77

5-[4-Methoxy-3-(3-(2-quinolinylmethoxy)phenoxymethyl)phenyl]tetrazole (M.P. 184-87°C)
CALC: C, 67.63; H, 4.88; N, 15.78
FOUND: C, 67.18; H, 5.13; N, 15.40

5-[3-(4-(2-quinolinylmethyloxy)phenoxymethyl)phenyl]tetrazole (M.P. 176-177°C)
CALC: C, 69.63; H, 4.75; N, 16.92
FOUND: C, 69.58, 69.64; H, 5.00, 4.98; N, 16.66, 16.63

5-[3-Methoxy-4-(4-(2-quinolinylmethyloxy)benzyloxy)phenyl]tetrazole (M.P. 195-97°C)
CALC: C, 67.63; H, 4.88; N, 15.77
FOUND: C, 67.27; H, 4.89; N, 15.41

5-[4-(3-(2-quinolinylmethyloxy)phenoxymethyl)-3methoxyphenyl]tetrazole (M.P. 189-91°C)
CALC: C, 66.95; H, 4.95; N, 15.61
FOUND: C, 66.48; H, 5.14; N, 14.93

5-[3-(4-(2-quinolinylmethyloxy)phenoxymethyl)benzyl]tetrazole (M.P. 139-44°C)
CALC: C, 70.53; H, 5.03; N, 16.45
FOUND: C, 70.33, 70.54; H, 5.25, 5.36; N, 16.38, 16.41

5-[4-(4-(2-quinolinylmethyloxy)phenoxymethyl)benzyl]tetrazole (M.P. 167-71°C)
CALC: C, 67.33; H, 5.31; N, 15.70
FOUND: C, 67.54, 67.67,; H, 5.33, 5.33; N, 15.48, 15.52

2-[4-(2-Quinolinylmethyloxy)phenoxymethyl]cinnamic acid (M.P. 175-178°C)

CALC: C, 75.90; H. 5.14; N. 3.40

FOUND: C, 73.92; H. 5.20; N. 3.01

CALC: C, 74.27; H. 5.27; N,3.33 (as Hydrate)

6-Acetyl-2-propyl-3-[3-(2-quinolinylmethyloxy)-benzyloxy]phenoxyacetic acid (M.P. 153-58°C)

CALC: C, 72.13; H, 5.85; N, 2.90

FOUND: C, 71.68, 72.08; H, 5.88, 5.83; N, 2.65, 2.70

2-[2-(4-(7-Chloroquinolin-2-ylmethyloxy)-phenoxymethyl)phenoxy]propionic acid (M.P. 169-173°C)

CALC: C, 67.32; H, 4.78; N, 3.02; CI, 7.64

FOUND: C, 65.18; H, 4.90; N, 2.84; CI, 8.33

CALC: C, 65.41; H, 4,96; N, 2.93; CI, 7.42 (as HYDRATE)

2-[4-(2-Quinolinylmethyloxy)phenoxymethyl]phenylacetic acid (M.P. 181-83°C)

CALC: C, 75.17; H, 5.30; N, 3.51

FOUND: C, 75.12, 74.96; H, 5.50, 5.49; N, 3.16, 3.16

3-[3-(2-Quinolinylmethyloxy)phenoxymethyl]phenoxyacetic acid (M.P. 146-51°C)

CALC: C, 72.28; H. 5.10; N. 3.37

FOUND: C, 71.82, 71.80; H. 5.24, 5.23; N, 2.98, 3.00

CALC: C, 71.50; H, 5.16; N, 3.34 (as HYDRATE)

2-[4-(2-Quinolinylmethyloxy)phenoxymethyl]phenoxyacetic acid (M.P. 153-57°C)

CALC: C, 72.28; H, 5.10; N, 3.37

FOUND: C, 72.30, 71.72; H, 5.39, 5.30; N, 2.94, 2.89

5-[2-(4-(7-Chloroquinolin-2-ylmethyloxy)-phenoxymethyl)benzyl]tetrazole (M.P. 159-63°C)

CALC: C, 65.57; H, 4.40; N, 15.29

2-[2-(4-(2-Quinolinylmethyloxy)phenoxymethyl)phenoxy]pentanoic acid (M.P. 85-92°C)

CALC: C, 73.51; H, 5.95; N, 3.06

FOUND: C, 71.73, 71.79; H, 5.96, 5.91; N, 3.06, 2.83

CALC: C, 72.09; H, 6.05; N, 3.00 (as HYDRATE)

2-Carbomethoxy-5-[4-(2-quinolinylmethyloxy)-phenoxymethyl]phenoxyacetic acid (M.P. 149-51°C)

CALC: C, 68.49; H, 4.90; N, 2.95

FOUND: C, 68.00, 68.08; H, 4.98, 5.04; N, 2.90, 2.90

2-[2-(4-(2-Quinolinylmethyloxy)phenoxymethylphenoxy]propionic acid (M.P. 161-64°C)

CALC: C, 72.71; H, 5.40; N, 3.26

FOUND: C, 70.96, 71.10; H, 5.51, 5.58; N, 3.08, 3.10

CALC: C, 71.22; H, 5.52; N, 3.19 (as HYDRATE)

2-[2-(3-(2-Quinolinylmethyloxy)phenoxymethyl)phenoxy]glutaric acid (M.P. 83°C dec)

CALC: C, 68.98; H, 5.17; N, 2.87

FOUND: C, 64.10, 63.75; H, 4.89, 4.92; N, 2.64, 2.69

CALC: C, 63.74; H, 5.63; N, 2.65(as HYDRATE)

2-(3-[2-Quinolinylmethyloxy]benzyloxy)phenoxyacetic acid (M.P. 153-55°C)

CALC: C, 72.28; H. 5.10; N. 3.37

FOUND: C, 71.75; H. 5.14; N. 3.38

CALC: C, 71.50; H. 5.16; N. 3.34 (as HYDRATE)

2-(2-[4-(2-Quinolinylmethyloxy)phenoxymethyl]-4chlorophenoxy)propionic acid (M.P. 196-99°C)

CALC: C, 67.32; H, 4.78; N, 3.02

FOUND: C, 67.40, 67.43; H, 4.89, 4.94; N, 3.01, 3.13

CALC: C, 68.36; H, 5.33; N, 2.85
FOUND: C, 68.10; H, 5.39; N, 2.72

2-(2-[3-(2-Quinolinylmethyloxy)phenoxymethyl]-6-chlorophenoxy)-4-methylpentanoic acid (M.P. 164-66°C)
CALC: C, 68.84; H, 5.58; N, 2.77
FOUND: C, 68.84; H, 5.70; N, 2.69

2-(2-[4-(2-Quinolinylmethyloxy)phenoxymethyl]-6-chlorophenoxy)-4-methylpentanoic acid (M.P. 167-69°C)
CALC: C, 68.84; H, 5.58; N, 2.77
FOUND: C, 68.78; H, 5.67; N, 2.68

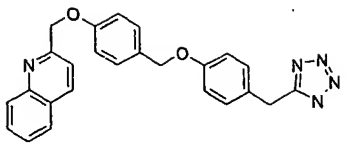
5-[3-(3-(2-quinolinylmethyloxy)benzyloxy)-4-methoxyphenyl]tetrazole (M.P. 204-07°C)
CALC: C, 67.63; H, 4.88; N, 15.78
FOUND: C, 67.11; H, 5.15; N, 15.86

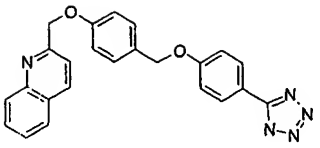
N-[3-Methoxy-4-(3-(2-quinolinylmethyloxy)benzyloxy)benzoyl)benzene sulfonamide hydrochloride (M.P. dec.88)
CALC: C, 62.99; H, 4.60; N, 4.74
FOUND: C, 63.88; H, 5.13; N, 4.80

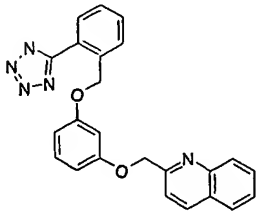
5-Carboxy-2-(3-(2-quinolinylmethyloxy)phenoxymethyl)phenoxy acetic acid (M.P. 226-28°C)
CALC: C, 61.90; H, 5.18; N, 2.77
FOUND: C, 61.62; H, 5.11; N, 2.67

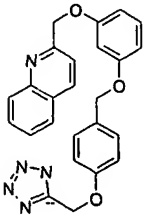
5-[3-Methoxy-4-(3-(2-quinolinylmethyloxy)benzyloxy)phenyl]tetrazole (M.P. 204-05°C)
CALC: C, 67.67; H, 5.14; N, 15.87
FOUND: C, 67.63; H, 4.88; N, 15.78

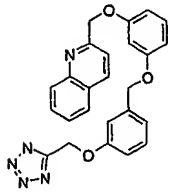
5-(4-(3-(2-Quinolinylmethyloxy)benzyloxy)phenyl)tetrazole (M.P. 233-36°C)

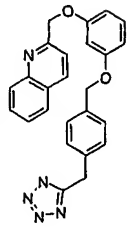
179-181°C  ;

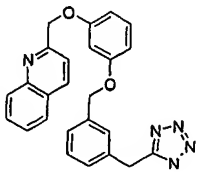
210-213°C  ;

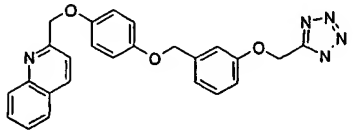
166-170°C  ;

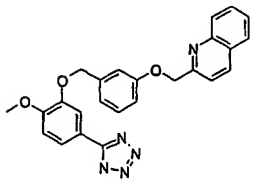
154-156°C  ;

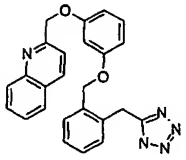
135-138°C  ;

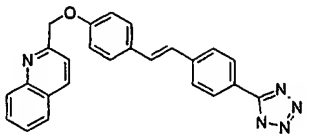
149-151°C  ;

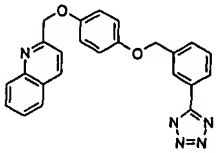
161-164°C  ;

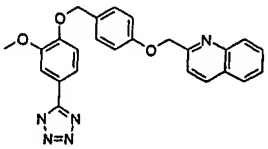
131-2°C (dec)  ;

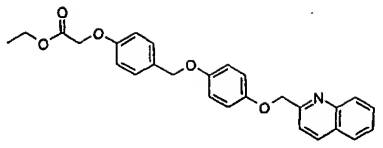
204-207°C  ;

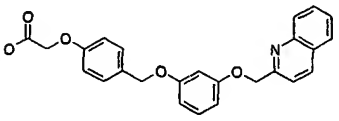
144-147°C  ;

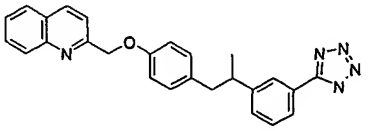
241-243°C  ;

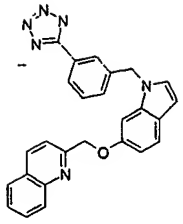
174-175°C  ;

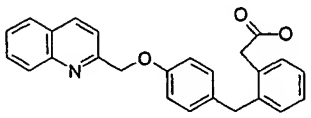
195-197°C  ;

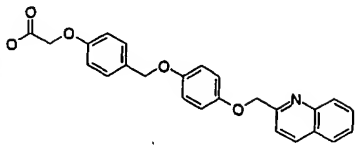
121-126°C  ;

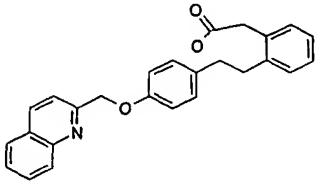
164°C (dec)  ;

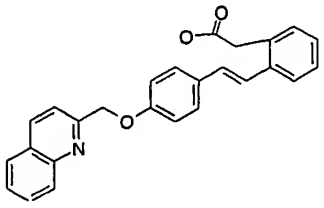
170-173°C  ;

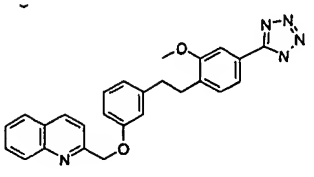
220-221°C  ;

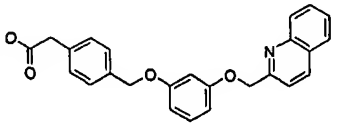
183-186°C  ;

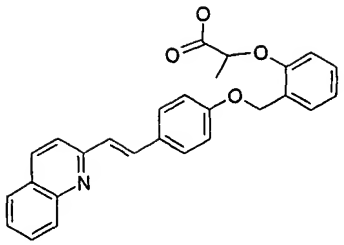
126°C (dec)  ;

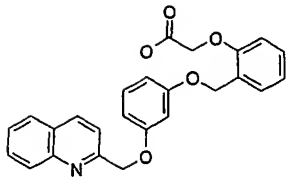
174-176°C  ;

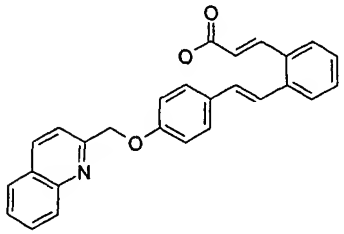
183-185°C  ;

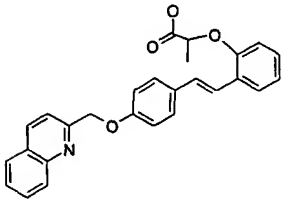
151-154°C  ;

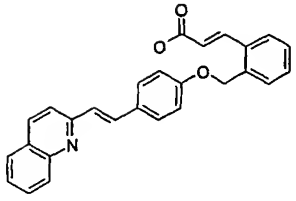
158-160°C  ;

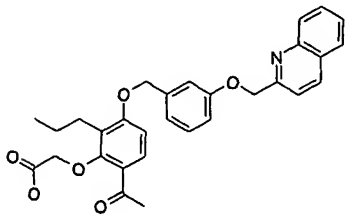
201-203°C  ;

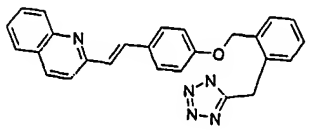
169-172°C  ;

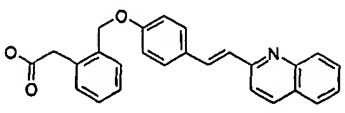
195-197°C  ;

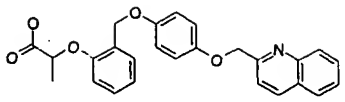
96-97°C  ;

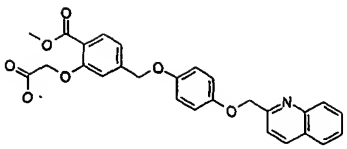
206-209°C  ;

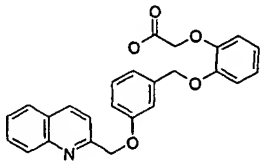
153-158°C  ;

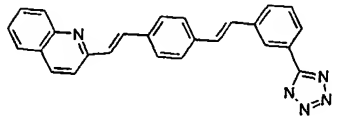
191-196°C  ;

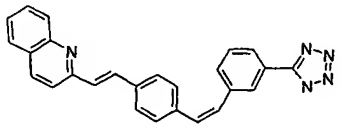
180-182°C  ;

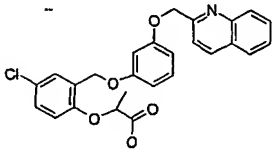
161-164°C  ;

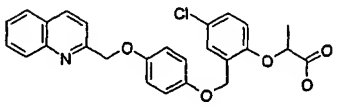
149-151°C  ;

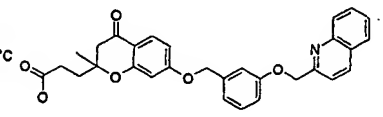
153-155°C  ;

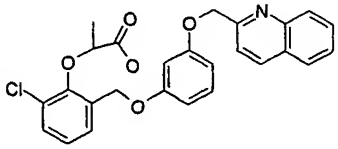
165-169°C  ;

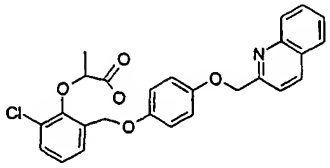
189-193°C  ;

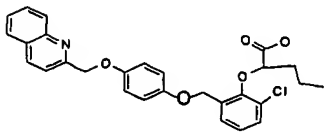
169-171°C  ;

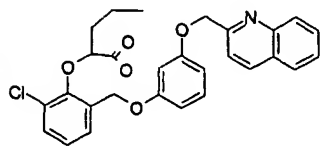
196-199°C  ;

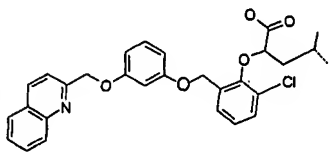
152-154°C  ;

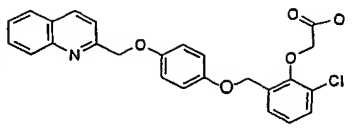
156-159°C  ;

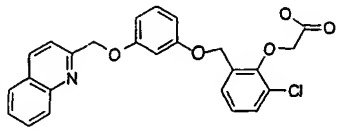
149-152°C  ;

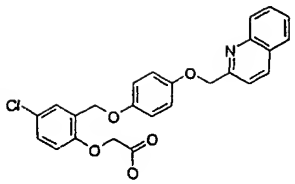
161-162°C  ;

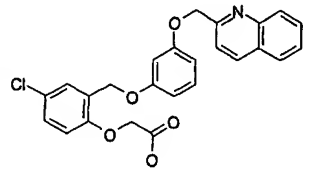
169-170°C  ;

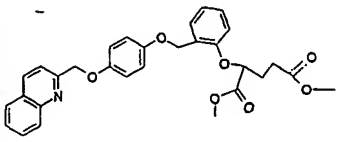
164-166°C  ;

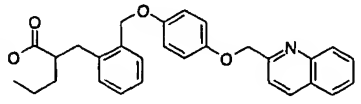
188-191°C  ;

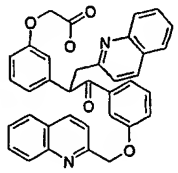
179-181°C  ;

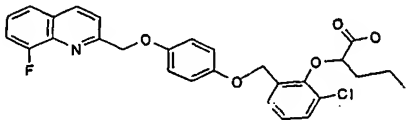
177-180°C  ;

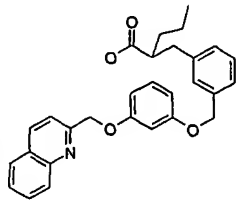
189-191°C  ;

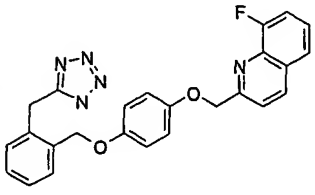
oil; CHN calc. C30H29NO7+0,5 H2O: C 68.69, H 5.76, N 2.67; found C 68.68, H 5.71, N 2.86  ;

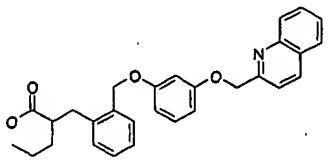
128-132°C  ;

104-106°C  ;

173-177°C  ;

CHN calc. C29H29NO + 0.75 H2O: C 74.26, H 6.55, N 2.99; found C 73.97, H 6.31, N 2.89  ;

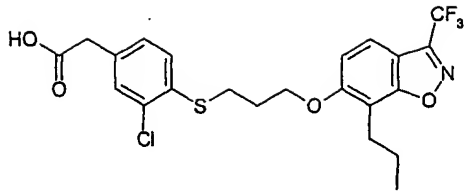
150-153°C  ;

101-103°C  ;

A binding assay for PPARα could be carried out by the following procedure: cDNAs encoding the putative ligand binding domain of human PPARα (amino acids 167-468) (Sher,T., Yi, H.-F., McBride, O. W.& Gonzalez, F. J. (1993) Biochemistry 32, 5598-5604) are amplified by PCR (Polymerase Chain Reaction) and inserted in frame into the BamHI site of pGEX-2T plasmid (Pharmacia). The soluble fraction of GST-hPPARα fusion proteins or glutathione S-transferase (GST) alone are overexpressed in E. coli BL21(DE3)pLysS cells and purified from bacteria extracts as described in (S. Kliewer, et al. Proc. Natl. Acad. Sci. USA 94 (1997), 4318-4323).

Gel-Filtration Assays: 30 ml of 90 nM GST-hPPARα-LBD is mixed with 20 ml of 50 nM ^{3}H-GW2331 with or without 5 ml of 10 mM test compounds in the binding buffer containing 10 mM Tris, 50 mM KCl, 0.05% Tween 20 and 10 mM DTT. The reaction mixtures are incubated in 96-well plates for 2h at room temperature. 50 ml of the reaction mixtures are then loaded on a 96-well gel filtration block (following manufacture instructions)(EdgeBioSystems). The block placed on top of a clean 96-well plate is centrifuged at 1,500 rpm for 2 min. The block is discarded. 100 ml of Scintillation fluid is added to each well of the 96-well plate. After overnight equilibration, the plate is counted in the Microbeta counter (Wallac.).

Homogenous Scintillation Proximity Binding Assay. For the Scatchard analysis, glutathione coated SPA beads (1.5 mg/ml)(Amersham) are mixed with GST-hPPARα-LBD (10 mg/ml) in the binding buffer. The resulting slurry is incubated at room temperature with agitation for 15 min. 20 ml of the slurry is then added in 30 ml of binding buffer containing various amount ^{3}H-GW2331(10~500 nM). Nonspecific binding is determined in the present of 100 mM of GW2331. For the competition binding assay, 20 ml of the slurry is then added in 30 ml of the binding buffer containing 75 nM of ^{3}H-GW2331 and 0.03~20 mM of the test compounds. For the control experiments, the glutathione coated SPA beads (1.5 mg/ml) are coated with GST proteins (10 mg/ml). 20 ml of the slurry are mixed with 30 ml of 75 nM of ^{3}H-GW2331 with or without 10 mM of GW2331. The above experiments are all performed in a 96-well plates. The sealed plates with the reaction mixtures are allowed to equilibrate for 2 h and counted in the Microbeta counter (Wallac.).



Compound X

The hPPARδ binding assay comprises the steps of:

(a) preparing multiple test samples by incubating separate aliquots of the receptor hPPARδ with a test compound in TEGM containing 5-10% COS-1 cell cytoplasmic lysate and 2.5 nM labeled ([^{3}H]Compound X, 17 Ci/mmol) for a minimum of 12 hours, and preferably for about 16 hours, at 4°C, wherein the concentration of the test compound in each test sample is different, and preparing a control sample by incubating a further separate aliquot of the receptor hPPARδ under the same conditions but without the test compound; then

(b) removing unbound ligand by adding dextran/gelatin-coated charcoal to each sample while maintaining the samples at 4°C and allowing at least 10 minutes to pass, then

(c) subjecting each of the test samples and control sample from step (b) to centrifugation at 4°C until the charcoal is pelleted; then

(d) counting a portion of the supernatant fraction of each of the test samples and the control sample from step (c) in a liquid scinitillation counter and analyzing the results to determine the IC_{50} of the test compound.

In the hPPARδ binding assay, preferably at least four test samples of varying concentrations of a single test compound are prepared in order to determine the IC_{50}.

ABC-1 Assays:

Assay Example 1 : ABC1 up-regulation in human THP-1 cell by PPAR mediators

THP-1 cells, a human monocytic cell line, are maintained in RPMI with 10% FCS (fetal calf serum)/ 20 mg/ml gentamycin/25 mM Hepes. Cells are plated at approximately 1 x 10^5 per cm^2 in RPMI/10% charcoal-stripped FCS (Hyclone) the presence or absence of 100 ng/ml PMA (phorbol myritic acid)(Gibco BRL) and the indicated concentrations of test compound or DMSO (dimethyl sulfoxide). Test compounds are refreshed daily. Alternatively, cells are incubated with 100 mg/ml AcLDL (acetylated LDL) as positive control. After 48 or 72 hours,

Assay Example 2 : ABC1 up-regulation in human hepatocytes and human macrophages derived monocytes by Fenofibric acid, and for Wy 14,643 and related cholesterol efflux in macrophages.

Cell Culture:

Mononuclear cells are isolated from blood of healthy normolipidemic donors (thrombopheresis residues). Monocytes isolated by Ficoll gradient centrifugation are suspended in RPMI 1640 medium containing gentamycin (40 mg/ml), glutamine (0.05%) (Sigma) and 10% of pooled human serum. Cells are cultured at a density of $3x10^6$ cells/well in 6-well plastic culture dishes (Primaria, Polylabo, France). Differentiation of monocytes into macrophages occured spontaneously by adhesion of cells to the culture dishes. Mature monocyte-derived macrophages as characterized by immunocytochemistry with anti CD-68 antibody, are used for experiments after 9 days of culture. For treatment with the different activators, medium is changed to RPMI 1640 medium without serum but supplemented with 1% Nutridoma HU (Boehringer Mannheim).

Human liver specimens are collected from healthy multiorgan donors for transplantation who died after severe traumatic brain injury. Hepatocytes are obtained by a two-step collagenase perfusion (REF). Cells are resuspended in minimal essential medium with Earl's salts with 10% FCS, 2 mM glutamine, 50 mg/ml gentamycin, seeded at density of $1.5x10^5$ cells/cm^2 in plastic culture dishes coated with 20 mg rat tail collagene type I (Sigma).Medium is renewed after 4 hours of adhesion. After 20 hours the medium is discarded and differents compounds added at the indicated concentrations in serum-free medium.

RNA extraction and analysis:

Total cellular RNA is extracted from differentated macrophages treated for 6 hours with different compounds using the RNA plus kit (Bioprobe System, Montreuil, france). RNA from human hepatocytes are prepared as described by Chomczynski and Sacchi. For RT-PCR analysis, total RNA is reverse transcribed using random hexamer primers and Superscript reverse transcriptase (Life Technologies) as sebsequently amplified by PCR. The resulting products are separated on a 1% agrose gel and stained with ethidium bromide.

Cholesterol loading and efflux:

9 days-old human macrophages are pretreated for 24 hours with different PPAR activators and cholesterol loaded by incubation with acetylated LDL (50µg of proteins in 2

The active compound may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be from about 2% to about 6% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 50 and 300 mg of active compound.

The tablets, troches, pills, capsules and the like may also contain the following: A binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens a preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and formulations.

The active compound may also be administered parenterally or intraperitoneally. Solutions of the active compound as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropyl-cellulose. Dispersion can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

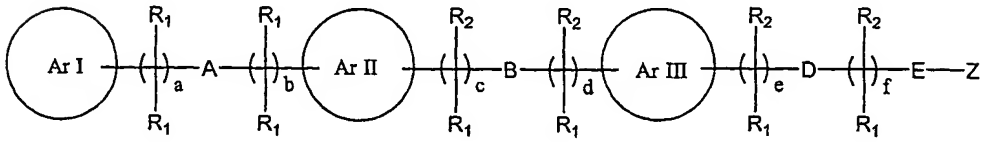
treatment. He will generally wish to initiate treatment with small dosages by small increments until the optimum effect under the circumstances is reached. The therapeutic dosage will generally be from 0.1 to 100 mM/day or from about 0.1mg to about 50 mg/kg of body weight per day, or 10mg to about 50 mg/kg of body weight per day, or more preferably 30mg to about 50 mg/kg of body weight per day, and higher, although it may be administered in several different dosage units. Higher dosages are required for oral administration.

The compounds useful according to the invention may be administered as frequently as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day. It goes without saying that, for other patients, it will be necessary to prescribe not more than one or two doses per day.

One skilled in the art will readily appreciate that the present invention is well adapted to carry out the objects of the invention and obtain the ends and advantages mentioned, as well as those inherent therein. The compounds, compositions and methods described herein are presented as representative of the preferred embodiments, or intended to be exemplary and not intended as limitations on the scope of the present invention.

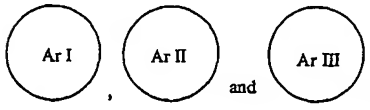
[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione, WAY-120,744, and Darglitazone and their pharmaceutically acceptable salts.

16. A method according to claim 1 or 9 wherein the PPAR mediator is a compound of formula (I)



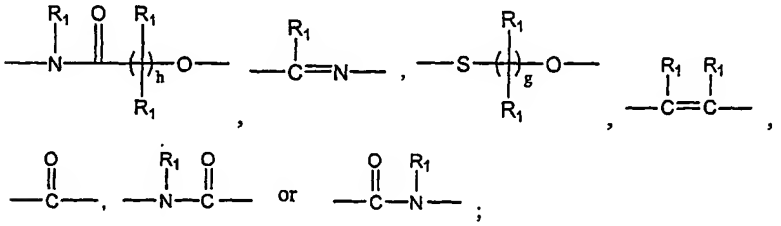
(I)

wherein:

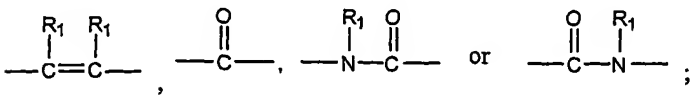


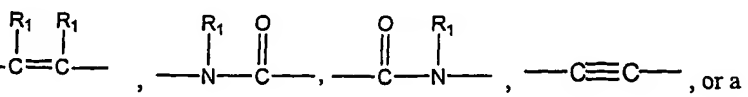
are independently aryl, fused arylcycloalkenyl, fused arylcycloalkyl, fused arylheterocyclenyl, fused arylheterocyclyl, heteroaryl, fused heteroarylcycloalkenyl, fused heteroarylcycloalkyl, fused heteroarylheterocyclenyl, or fused heteroarylheterocyclyl;

A is O, S, SO, SO_2, NR_5, a chemical bond,



B is O, S, SO, SO_2, NR_4, a chemical bond,



D is O, S, NR_4,  or a chemical bond;

E is a chemical bond or

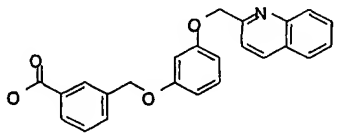
Z is R_3O_2C-, R_3OC-, cyclo-imide, -CN, R_3O_2SHNCO-, R_3O_2SHN-, $(R_3)_2NCO$-,R_3O- or tetrazolyl; and

R_3 and R_4 are independently hydrogen, alkyl, aryl, cycloalkyl, or aralkyl;

R_5 is R_6OC-, R_6NHOC-, hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, heteroaralkyl, or aralkyl; and

R_6 is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, heteroaralkyl, or aralkyl; or a pharmaceutically acceptable salt thereof.

17. A method according to claim 1 or 9 wherein the PPAR mediator is selected from the group consisting of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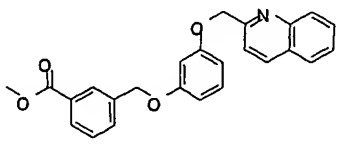
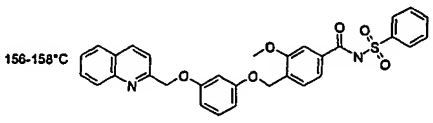

;

208-210°C


156-158°C
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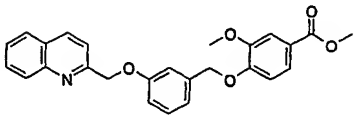
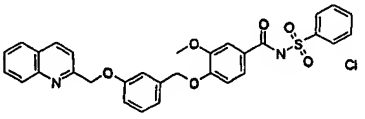
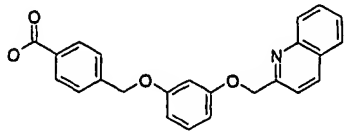

100-101°C
;

88°C (dec)
;
;


190-192°C
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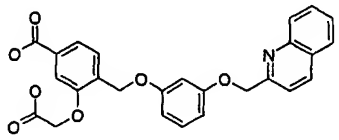
226-228°C
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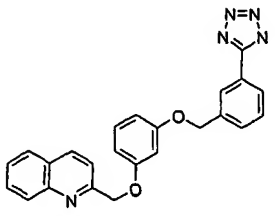
115°C (dec)
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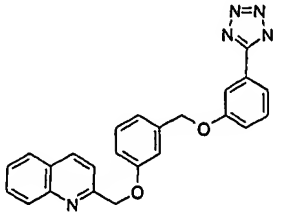
169-172°C
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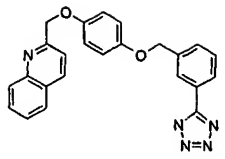
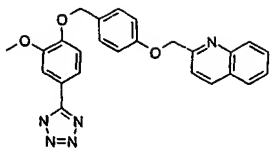
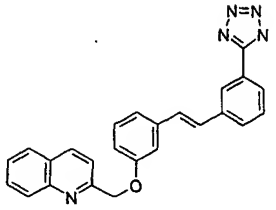
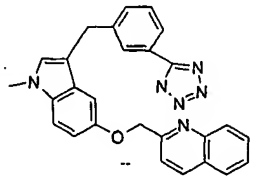
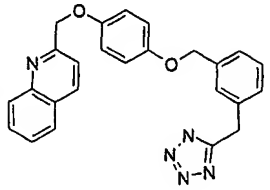
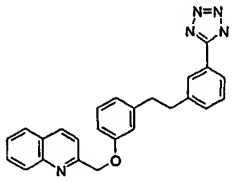
174-175°C  ;

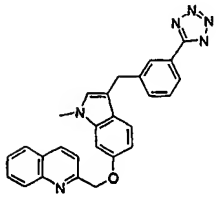
195-197°C  ;

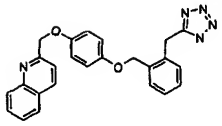
117-118°C  ;

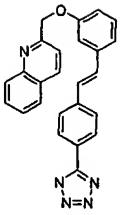
78-80°C  ;

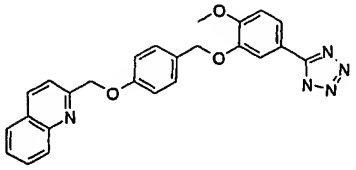
139-144°C  ;

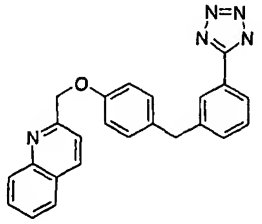
126-129°C  ;

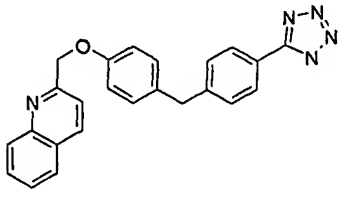
181-183°C  ;

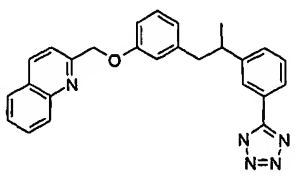
152-155°C  ;

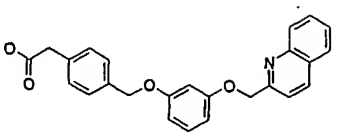
223-224°C  ;

210-213°C  ;

186-189°C  ;

206-209°C  ;

83-86°C  ;

158-160°C 

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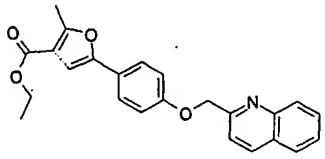
110°C 

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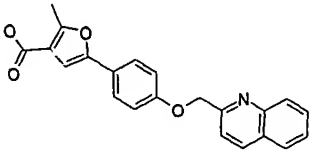
230-231°C 

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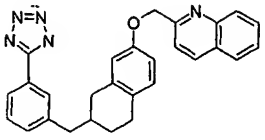
116-118°C 

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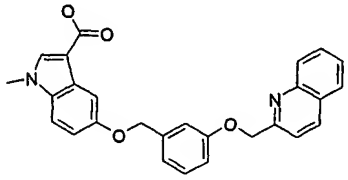
197-199°C 

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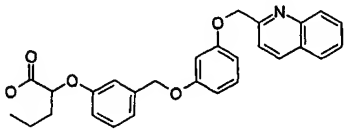
135-137°C 

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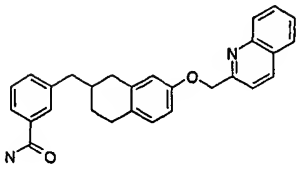
162-164°C 

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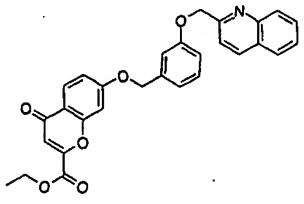
123-124°C 

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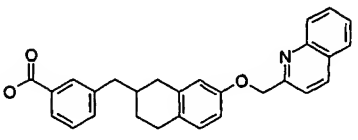
156-158°C 

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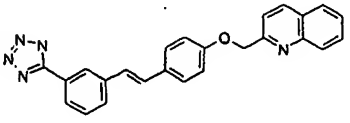
50-51°C 

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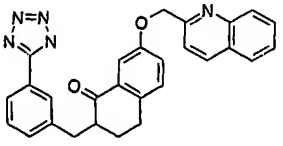
187-188°C 

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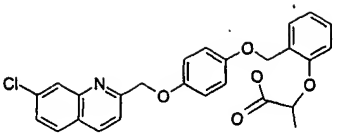
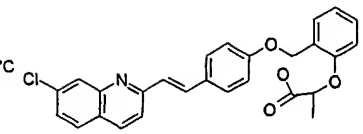
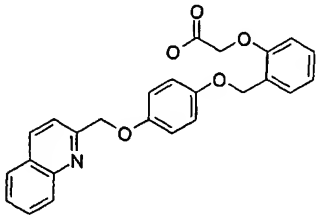
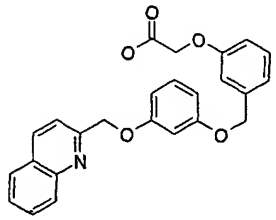
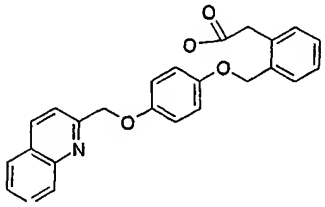
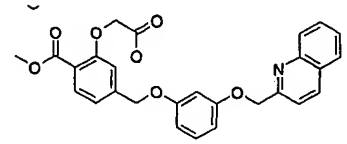
169-173°C  ;

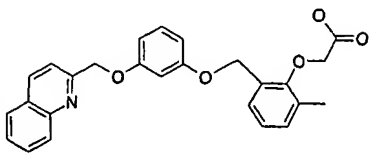
237-239°C  ;

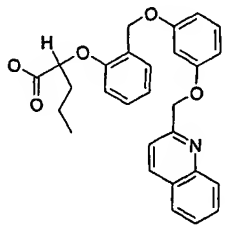
153-157°C  ;

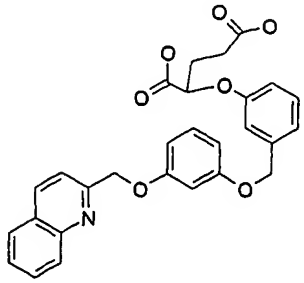
146-151°C  ;

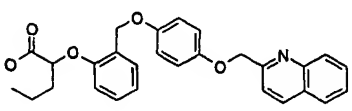
181-183°C  ;

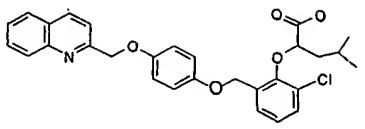
187-189°C  ;

149-153°C  ;

118-120°C  ;

129-130°C  ;

85-92°C  ;

167-169°C 

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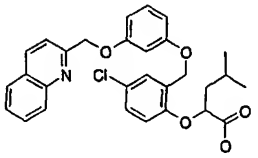
123-125°C 

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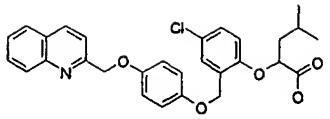
143-147°C 

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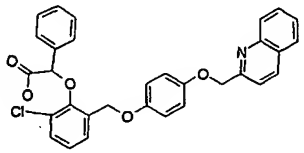
76-87°C 

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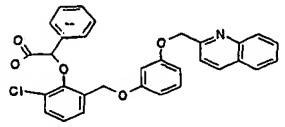
156-157°C 

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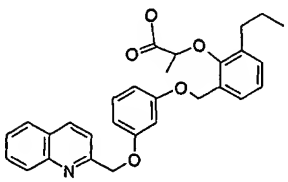
150-157°C 

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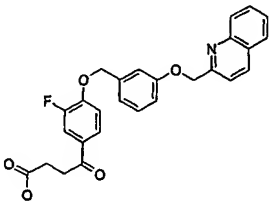
145-147°C 

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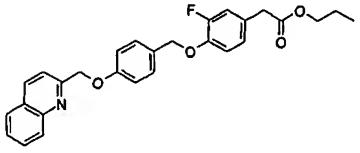
107°C 

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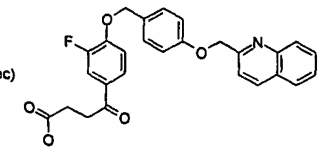
187°C (dec) 

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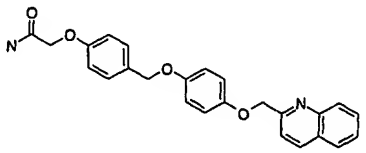
182-184°C 

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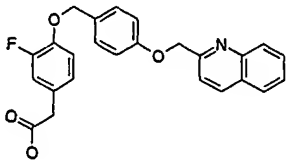
173-4°C (dec) 

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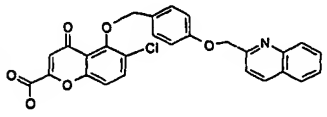
173-5°C (dec) 

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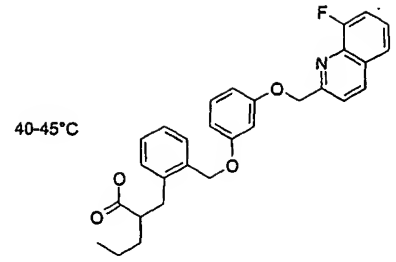
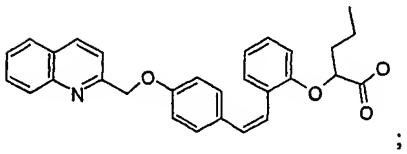


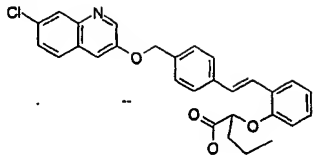
40-45°C

;103-106°C



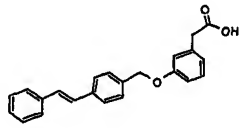
;

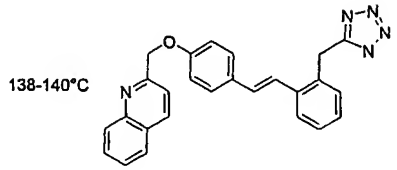
60-63°C



;

190-193°C

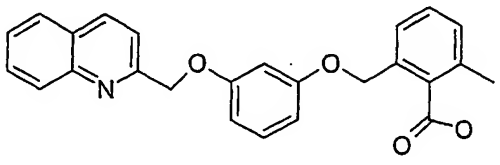




138-140°C

; and

18. A method according to claim 1 or 9 wherein the PPAR mediator is selected from the group consisting of



; and

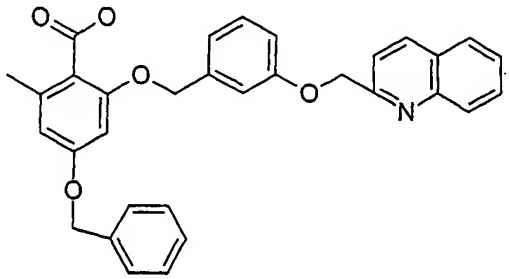


Fig. 1

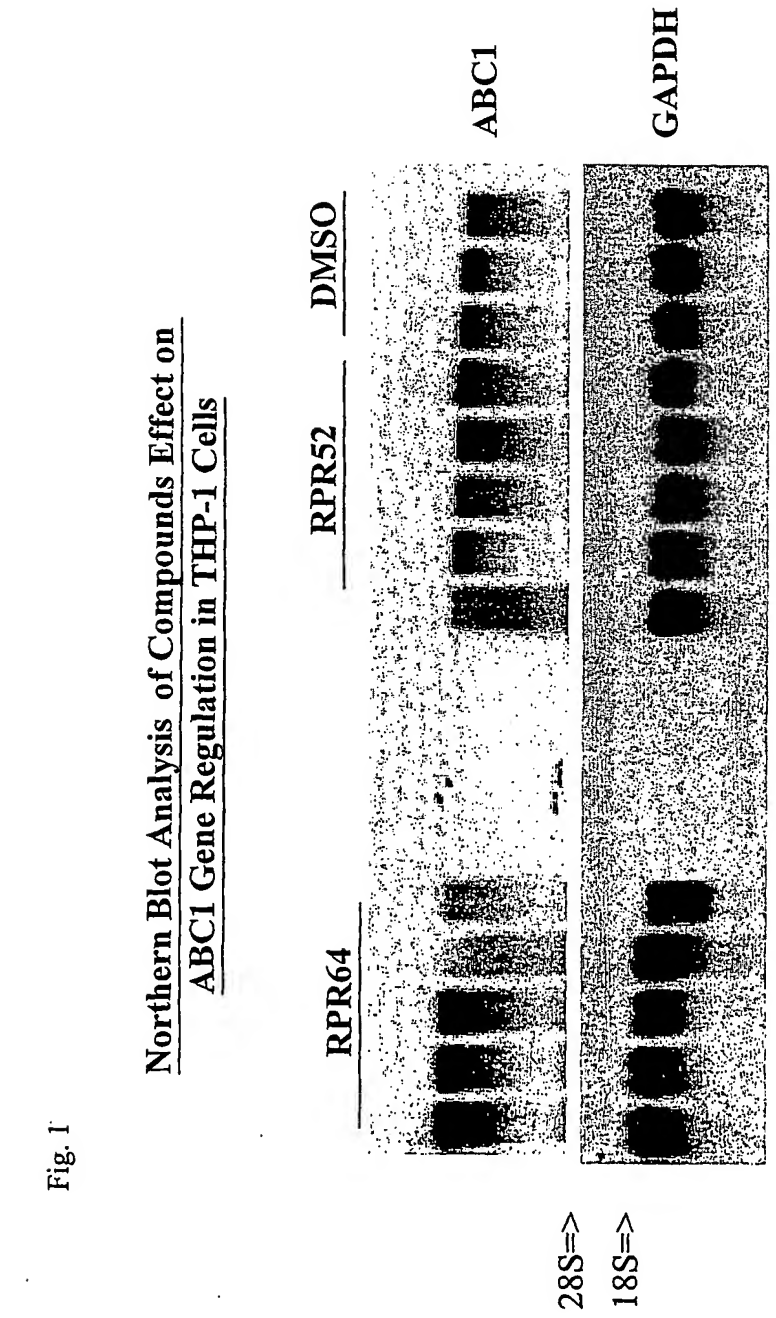
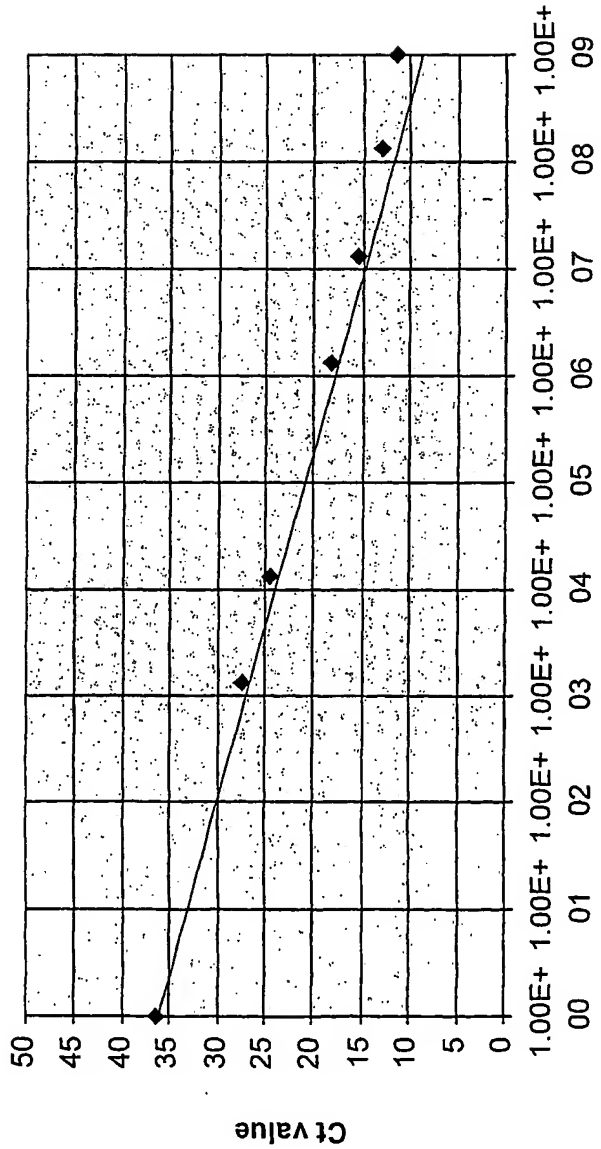


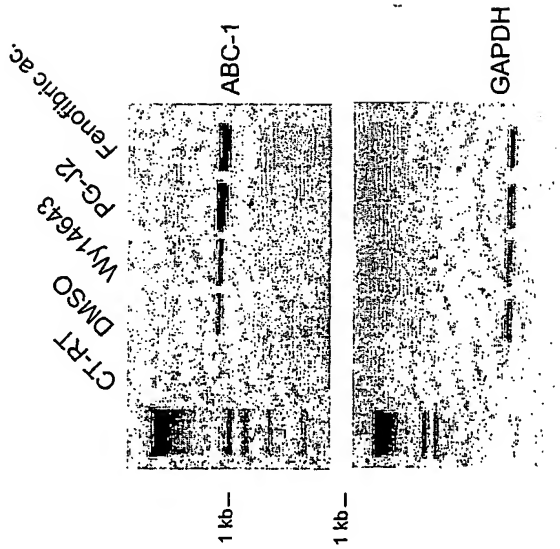
Fig. 3: ABC1 standard curve with TaqMan 5P primer/probe set



Slope: -2.766; Y-intercept: 36.04; Correlation Coefficient: 0.970

Fig. 5

REGULATION OF ABC-1 BY PPAR ACTIVATORS IN HUMAN MACROPHAGES



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(57) Abstract: Use of PPAR mediators, and their pharmaceutical compositions, as ATP binding cassette transporter 1 (ABC-1) expression modulators, wherein the PPAR ligand receptor agonists of this invention are useful as inducers of ABC-1 expression.

INTERNATIONAL SEARCH REPORT

Interna ll Application No
PCT/EP 01/02482

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US 5 861 274 A (BLUMBERG BRUCE ET AL) 19 January 1999 (1999-01-19) abstract example 7 column 14, line 48 - line 59	12,14, 15,17-19
P,X	WO 00 76488 A (NATHWANI AMEET :SMITHKLINE BEECHAM PLC (GB)) 21 December 2000 (2000-12-21) abstract page 1, line 2 - line 14 page 16, line 16 - line 23 claims 1-11	12,14,15
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